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(54) **CRYSTALLINE POLYMORPH OF THE FREE BASE OF 2-HYDROXY-6-((2-(1-ISOPROPYL-1H-PYRAZOL-5-YL)PYRIDIN-3-YL)METHOXY)BENZALDEHYDE**

KRISTALLINES POLYMORPH DER FREIEN BASE VON 2-HYDROXY-6-((2-(1-ISOPROPYL-1H-PYRAZOL-5-YL)PYRIDIN-3-YL)METHOXY)BENZALDEHYD

POLYMORPHE CRISTALLIN DE LA BASE LIBRE DE 2-HYDROXY-6-((2-(1-ISOPROPYL-1H-PYRAZOL-5-YL)PYRIDIN-3-YL)MÉTHOXY)BENZALDÉHYDE

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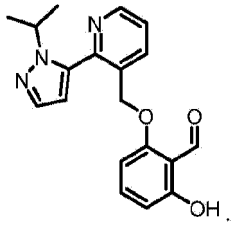
EP 3 102 208 B2

Description

Background

[0001] 2-Hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde is a compound having the formula:



[0002] Sickle cell disease is a disorder of the red blood cells, found particularly among those of African and Mediterranean descent. The basis for sickle cell disease is found in sickle hemoglobin (HbS), which contains a point mutation relative to the prevalent peptide sequence of hemoglobin (Hb).

[0003] Hemoglobin (Hb) transports oxygen molecules from the lungs to various tissues and organs throughout the body. Hemoglobin binds and releases oxygen through conformational changes. Sickle hemoglobin (HbS) contains a point mutation where glutamic acid is replaced with valine, allowing HbS to become susceptible to polymerization to give the HbS containing red blood cells their characteristic sickle shape. The sickled cells are also more rigid than normal red blood cells, and their lack of flexibility can lead to blockage of blood vessels. A need exists for therapeutics that can treat disorders that are mediated by Hb or by abnormal Hb such as HbS, such as 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde.

[0004] When used for treating humans, it is important that a crystalline form of a therapeutic agent, like 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde, or a salt thereof, retains its polymorphic and chemical stability, solubility, and other physicochemical properties over time and among various manufactured batches of the agent. If the physicochemical properties vary with time and among batches, the administration of a therapeutically effective dose becomes problematic and may lead to toxic side effects or to ineffective therapy, particularly if a given polymorph decomposes prior to use, to a less active, inactive, or toxic compound. Therefore, it is important to choose a form of the crystalline agent that is stable, is manufactured reproducibly, and has physicochemical properties favorable for its use as a therapeutic agent.

[0005] However, the art remains unable to predict which crystalline form of an agent will have a combination of the desired properties and will be suitable for human administration, and how to make the agent in such a crystalline form. WO 2013/102142 and US 2013/190315 relate to "substituted benzaldehydes and derivatives thereof that act as allosteric modulators of hemoglobin, methods and intermediates for their preparation, pharmaceutical compositions comprising the modulators, and methods for their use in treating disorders mediate by hemoglobin and disorders than would benefit from increase tissue oxygenation."

Summary

Ansolvates

[0006] This invention arises in part out the discovery that an HCl salt of Compound 1 disproportionates or loses HCl, and a disproportionation of the HCl salt of Compound 1 in water generates the free base and disproportionation was facile upon exposure to elevated humidity, with wet milling, and in direct contact with water (e.g. slurry). The sulfate salt of Compound 1 also disproportionates from certain solvents such as dimethyl sulfoxide and methanol when precipitated with water. The volatilization of HCl was evident within hours of exposure to drying conditions. For example, partial conversion to the free base was observed within 12 hours at 30 °C. Accordingly, the free base of Compound 1 provides a stabler chemical entity compared to the corresponding HCl or sulfate and such other salt.

[0007] It has now been discovered that 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (or Compound 1) i.e., the free base of Compound 1, can be obtained as one or more crystalline ansolvate forms, several of which are referred to here as crystalline Form I, Form II and Material N (Form I and Material N are not according to the invention). In preferred embodiments, the free base of Compound 1 is a crystalline ansolvate, such as a crystalline anhydrous form. The free base of Compound 1, can be obtained from its corresponding salt form, such as the HCl salt of Compound 1.

[0008] Three anhydrous crystalline forms of the free base were identified, termed Free Base Forms I, II, and Material N. It has been discovered that nucleation of Free Base Form I generally occurs first from a slurry. Extending the slurry time can induce the transformation of Free Base Form I to Free Base Form II, a thermodynamically more stable phase relative to Form I. It has further been discovered that Free Base Material N can be stable relative to Forms I and II, at room temperature.

[0009] Free Base Material N was found to be enantiotropically related to Form II, and will transform reversibly at a specific transition temperature (estimated herein near 40-42 °C). Above the transition temperature, Free Base Form II appears to be the most stable form, relative to Form I and Material N. Thus, under operating temperatures below 40 °C, e.g., at 30 °C, the free base of Compound 1 exists primarily as Material N, which may have some residual Form II. Thus, at operating temperatures above 40 °C, e.g., at 50 °C, the free base of Compound 1 exists primarily as Form II, which may have some residual Material N. At 40 °C little appreciable conversion is seen between Material N and Form II. This is contemplated to be true for slurries of the free base in certain solvents and in the solid state. In one embodiment, the one or more crystalline free base forms of Compound 1 do not undergo polymorphic transformation under conditions suitable for manufacturing and storing the crystalline forms.

Form I (not according to the invention)

[0010] In one embodiment, the crystalline free base of Compound 1 comprises crystalline Form I, which is characterized by an endothermic peak at (97±2) C as measured by differential scanning calorimetry. In another embodiment, the crystalline Form I of the free base of crystalline Compound 1 is characterized by the substantial absence of thermal events at temperatures below the endothermic peak at (97±2) °C as measured by differential scanning calorimetry. In another embodiment, the crystalline Form I of the free base of crystalline Compound 1 is characterized by an X-ray powder diffraction peak (Cu Kα radiation at one or more of 12.82°, 15.74°, 16.03°, 16.63°, 17.60°, 25.14°, 25.82° and 26.44° ±0.2 °2θ. In another embodiment, the crystalline Form I of the free base of crystalline Compound 1 is characterized by an X-ray powder diffraction pattern (Cu Kα radiation) substantially similar to that of FIG. 3.

[0011] In another embodiment, the crystalline Form I of the free base of crystalline Compound 1 is characterized by at least one X-ray powder diffraction peak (Cu Kα radiation) selected from 12.82°, 15.74°, 16.03°, 16.63°, 17.60°, 25.14°, 25.82° and 26.44° (each ±0.2 °2θ). In another embodiment, the crystalline Form I of the free base of crystalline Compound 1 is characterized by at least two X-ray powder diffraction peaks (Cu Kα radiation) selected from 12.82°, 15.74°, 16.03°, 16.63°, 17.60°, 25.14°, 25.82° and 26.44° (each ±0.2 °2θ). In another embodiment, the crystalline Form I of the free base of crystalline Compound 1 is characterized by at least three X-ray powder diffraction peaks (Cu Kα radiation) selected from 12.82°, 15.74°, 16.03°, 16.63°, 17.60°, 25.14°, 25.82° and 26.44° (each ±0.2 °2θ).

[0012] In another embodiment, Form I is characterized by 1, 2, 3, 4, or more peaks as tabulated below.

Observed peaks for Form I, XRPD file 609973.

°2θ	*d* space (Å)	Intensity (%)
5. 52 ± 0.20	16.021 ± 0.602	68
12.82 ± 0.20	6.906 ± 0.109	74
15.03 ± 0.20	5.897 ± 0.079	38
15.74 ± 0.20	5.629 ± 0.072	46
16.03 ± 0.20	5.530 ± 0.069	46
16.63 ± 0.20	5.331 ± 0.064	61
17.60 ± 0.20	5.040 ± 0.057	100
18.74 ± 0.20	4.736 ± 0.051	24
19.07 ± 0.20	4.654 ± 0.049	17
19.35 ± 0.20	4.587 ± 0.047	23
20.32 ± 0.20	4.370 ± 0.043	18
21.64 ± 0.20	4.106 ± 0.038	23
22.80 ± 0.20	3.901 ± 0.034	26
23.28 ± 0.20	3.821 ± 0.033	34
25.14 ± 0.20	3.543 ± 0.028	52
25.82 ± 0.20	3.451 ± 0.026	81
26.44 ± 0.20	3.371 ± 0.025	51
27.91 ± 0.20	3.197 ± 0.023	17
28.19 ± 0.20	3.165 ± 0.022	26

Form II

[0013] The invention provides the crystalline Compound 1 free base named crystalline Form II, which is characterized by an endothermic peak at (97±2) C as measured by differential scanning calorimetry. In another embodiment, the crystalline Form II of the free base of crystalline Compound 1 is characterized by the substantial absence of thermal events at temperatures below the endothermic peak at (97±2) °C as measured by differential scanning calorimetry. In another embodiment, the crystalline Form II of the free base of crystalline Compound 1 is characterized by an X-ray powder diffraction peak (Cu Kα radiation at 13.37°, 14.37°, 19.95° and 23.92 °2θ. In another embodiment, the crystalline Form II of the free base of crystalline Compound 1 is characterized by an X-ray powder diffraction pattern (Cu Kα radiation) substantially similar to that of FIG. 5.

[0014] In another embodiment, the crystalline Form II of the free base of crystalline Compound 1 is characterized by at least one X-ray powder diffraction peak (Cu Kα radiation) selected from 13.37°, 14.37°, 19.95° and 23.92°2θ (each ±0.2 °2θ). In another embodiment, the crystalline Form II of the free base of crystalline Compound 1 is characterized by at least two X-ray powder diffraction peaks (Cu Kα radiation) selected from 13.37°, 14.37°, 19.95° and 23.92°2θ (each ±0.2 °2θ). In another embodiment, the crystalline Form II of the free base of crystalline Compound 1 is characterized by at least three X-ray powder diffraction peaks (Cu Kα radiation) selected from 13.37°, 14.37°, 19.95° and 23.92°2θ (each ±0.2 °2θ).

[0015] In another embodiment, Form II is characterized by 1, 2, 3, 4, or more peaks as tabulated below.

Observed peaks for Form II, XRPD file 613881.

°2θ	*d* space (Å)	Intensity (%)
5.62 ± 0.20	15.735 ± 0.581	24
12.85 ±0.20	6.888 ± 0.108	22
12.97 ± 0.20	6.826 ± 0.106	21
13.37 ± 0.20	6.622 ± 0.100	100
14.37 ± 0.20	6.162 ± 0.087	56
15.31 ±0.20	5.788 ± 0.076	21
16.09 ± 0.20	5.507 ± 0.069	23
16.45 ± 0.20	5.390 ± 0.066	69
16.75 ±0.20	5.294 ± 0.064	32
16.96 ± 0.20	5.227 ± 0.062	53
19.95 ± 0.20	4.450 ± 0.045	39
20.22 ± 0.20	4.391 ± 0.043	20
23.18 ± 0.20	3.837 ± 0.033	38
23.92 ± 0.20	3.721 ± 0.031	41
24.40 ± 0.20	3.648 ± 0.030	44
24.73 ± 0.20	3.600 ± 0.029	22
24.99 ± 0.20	3.564 ± 0.028	50
25.12 ± 0.20	3.545 ± 0.028	28
25.39 ± 0.20	3.509 ± 0.027	51
25.70 ± 0.20	3.466 ± 0.027	21
26.19 ± 0.20	3.403 ± 0.026	27
26.72 ± 0.20	3.336 ± 0.025	30
27.02 ± 0.20	3.300 ± 0.024	25
27.34 ± 0.20	3.262 ± 0.024	23
28.44 ± 0.20	3.138 ± 0.022	20

[0016] In some embodiments, the free base of crystalline Compound 1 comprises the crystalline Form II. In some preferred embodiments, the free base of crystalline Compound 1 comprises the crystalline Form II and less than 25 mole %, 10 mole % or 5 mole % of crystalline Form I, crystalline Material N or amorphous forms of Compound 1.

[0017] In a preferred embodiment, the crystalline Form II is prepared from a slurry comprising the free base of Compound 1 in heptane, from which the crystalline Form II is formed and filtered. Thus, in some embodiments, the crystalline Form II comprises residual (1-500 ppm) heptane. In another preferred embodiment, the crystalline Form II is prepared from a slurry comprising the free base of Compound 1 in water, from which the crystalline Form II is formed and filtered.

[0018] There are several advantages of crystalline Form II relative to crystalline Form I or Material N. For example, the crystalline Form II can be prepared from a slurry comprising the free base of Compound 1 in heptane, which is suitable for good manufacturing practices (GMP) protocols. Further, in a most preferred embodiment, the crystalline Form II can be prepared from a slurry comprising the free base of Compound 1 in water or the HCl salt of Compound 1 in water, thus reducing or eliminating the need for solvent during recrystalization. Thus, in some embodiments, crystalline Form II of Compound 1 comprises less than 500 ppm, 100 ppm, less than 50 ppm or less than 10 ppm organic solvent. Also, Form II has less of a propensity than Material N to agglomerate upon size reduction, e.g., upon milling. As such, Form II has greater flowability than Material N. Certain illustrative and non-limiting advantages of Form II over Material N (*i.e.*, Form N) are shown in the table below.

DATA/EXPERIMENT	RESULTS/STATUS
Identify suitable solvent for scale-up	Form N: • Limited number of suitable solvents compared to Form II • MTBE identified (suitable for GMP; Class III solvent) • Scale-up results look good Form II: • More solvent options than Form N, including H_2O • Current solvent is heptane (suitable for GMP; Class III solvent) • produced on 5 kg scale • Formation time faster than N (could translate to 2-3 day saving in production time) • Better recovery than N
Size/Morphology of N and II	• Acicular morphology observed for form N; material composed of small and large particles • Agglomerates are an issue for Form N relative to Form II (less agglomeration seen with energy-reduced method)
PK Comparison of N and II	• Oral administrations of GBT440 Forms N and II to rats resulted in comparable exposure at 100 & 500 mg/kg

Material N (not according to the invention)

[0019] In another embodiment, the crystalline Compound 1 free base comprises crystalline Material N, which is characterized by an endothermic peak at (95±2) C as measured by differential scanning calorimetry. The terms "Material N", "form N" and "polymorphic form N" are used interchangeably herein. In another embodiment, the crystalline Material N of the free base of crystalline Compound 1 is characterized by the substantial absence of thermal events at temperatures below the endothermic peak at (95±2) °C as measured by differential scanning calorimetry. In another embodiment, the crystalline Material N of the free base of crystalline Compound 1 is characterized by an X-ray powder diffraction peak (Cu Kα radiation at one or more of 11.65°, 11.85°, 12.08°, 16.70°, 19.65° or 23.48 °2θ. In another embodiment, the crystalline Material N of the free base of crystalline Compound 1 is characterized by an X-ray powder diffraction pattern (Cu Kα radiation) substantially similar to that of FIG. 7.

[0020] In another embodiment, the crystalline Material N of the free base of crystalline Compound 1 is characterized by at least one X-ray powder diffraction peak (Cu Kα radiation) selected from 11.65°, 11.85°, 12.08°, 16.70°, 19.65° and 23.48 °2θ (each ±0.2 °2θ). In another embodiment, the crystalline Material N of the free base of crystalline Compound 1 is characterized by at least two X-ray powder diffraction peaks (Cu Kα radiation) selected from 11.65°, 11.85°, 12.08°, 16.70°, 19.65° and 23.48 °2θ (each ±0.2 °2θ). In another embodiment, the crystalline Material N of the free base of crystalline Compound 1 is characterized by at least three X-ray powder diffraction peaks (Cu Kα radiation) selected from 11.65°, 11.85°, 12.08°, 16.70°, 19.65° and 23.48 °2θ (each ±0.2 °2θ).

[0021] In another embodiment, Material N is characterized by 1, 2, 3, 4, or more peaks as tabulated below.

Observed peaks for Material N, XRPD file 615765.

°2θ	*d* space (Å)	Intensity (%)
5.55 ± 0.20	15.924 ± 0.595	54
11.65 ± 0.20	7.597 ± 0.132	31
11.85 ± 0.20	7.468 ± 0.128	50

(continued)

°2θ	*d* space (Å)	Intensity (%)
12.08 ±0.20	7.324 ±0.123	31
12.67 ± 0.20	6.987 ± 0.112	29
13.12 ± 0.20	6.748 ± 0.104	83
14.94 ± 0.20	5.929 ± 0.080	34
15.19 ± 0.20	5.832 ± 0.077	56
15.76 ± 0.20	5.623 ± 0.072	20
16.70 ± 0.20	5.310 ± 0.064	100
17.35 ± 0.20	5.112 ± 0.059	52
19.65 ± 0.20	4.517 ± 0.046	60
23.48 ± 0.20	3.789 ± 0.032	72
23.68 ± 0.20	3.757 ± 0.032	29
25.25 ± 0.20	3.527 ± 0.028	20
25.47 ± 0.20	3.497 ± 0.027	20
25.70 ± 0.20	3.466 ± 0.027	85
26.04 ± 0.20	3.422 ± 0.026	35
26.37 ± 0.20	3.380 ± 0.025	55

[0022] In some embodiments, the free base of crystalline Compound 1 comprises the crystalline Material N and less than 25 mole %, 10 mole % or 5 mole % of crystalline Forms I or II or amorphous forms of Compound 1.

[0023] In another embodiment, the crystalline Material N is prepared from a slurry comprising the free base of Compound 1 in methyl tertiary butyl ether (MTBE), from which the crystalline - Material N is formed and filtered. Thus, in some embodiments, the crystalline Material N comprises residual (1-500 ppm) MTBE.

[0024] There are several advantages of crystalline Material N relative to crystalline Forms I or II. For example, the crystalline Material N can be prepared from a slurry comprising the free base of Compound 1 in MTBE, which is suitable for good manufacturing practices (GMP) protocols.

[0025] In some embodiments, the crystalline ansolvate forms are stable to contact with water, heptane, iso propyl ether (IPE), MTBE, and toluene, and such other solvents.

[0026] In another of its composition embodiments, this invention provides for a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a crystalline Compound 1 free base, comprising Form II.

[0027] In one of its method embodiments, this disclosure provides a method of preparing the solid crystalline free base of Compound 1 comprising, e.g., Form I, Form II and/or Material N.

[0028] The crystalline Form II of the free base of Compound 1 of the claims can be used in methods for increasing oxygen affinity of hemoglobin S in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of the crystalline Form II of the free base of Compound 1 of the claims.

[0029] The crystalline Form II of the free base of Compound 1 of the claims can be used in methods for treating oxygen deficiency associated with sickle cell anemia in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of the crystalline Form II of the free base of Compound 1 of the claims.

[0030] In all of such treatments, the effective amount of the crystalline Form II of the free base of Compound 1 of the claims to the treated patient is already disclosed in the art.

Solvates

[0031] This invention arises in part out of the discovery that ansolvate polymorphs of the free base of Compound 1 form solvate polymorphs with a variety of solvents, preferably other than certain hydrocarbon solvents, water and ethers.

[0032] Solvates of the crystalline free base of Compound 1 (e.g., from acetone, acetonitrile, dichloromethane, dioxane, ethanol, ethyl acetate, isopropyl alcohol, methyl ethyl ketone (MEK) and tetrahydrofuran) are also contemplated to be used e.g., as intermediates to regenerate the free base crystalline ansolvate of Compound 1. Such methods can include, without limitation, subjecting the solvate to vacuum conditions; and/or generating a salt and disproportionating it in water to form the ansolvate ; and/or slurrying or washing the solvate with a solvent less prone to solvate formation such as heptane, di-isopropyl ether (IPE), tert-methyl butyl ether (MTBE) and toluene.

[0033] In another of its composition embodiments, this invention provides for a pharmaceutical composition comprising a pharmaceutically acceptable excipient and Form II, as provided herein.

[0034] In one of its method embodiments, this disclosure provides a method of preparing the solvated crystal forms

provided herein.

[0035] The crystalline Form II of the free base of Compound 1 of the claims can be used in methods for increasing oxygen affinity of hemoglobin S in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of the crystalline Form II of the free base of Compound 1 of the claims.

[0036] The crystalline Form II of the free base of Compound 1 of the claims can be used in methods for treating oxygen deficiency associated with sickle cell anemia in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of the crystalline Form II of the free base of Compound 1 of the claims.

[0037] In all of such treatments, the effective amount of the crystalline Form II of the free base of Compound 1 of the claims, to the treated patient is already disclosed in the art.

Brief Description of the Drawings

[0038]

FIG. 1 is a XRPD profile of the crystalline HCl salt before (top) and after (bottom) 5 minutes slurried in water.

FIG. 2 is a XRPD profile of the free base Form I (top), Form II (middle), and Material N (bottom).

FIG. 3 is a XRPD profile and contemplated indexing for free base Form I.

FIG. 4 is a thermal characterization for free base Form I.

FIG. 5 is a XRPD profile and contemplated indexing for free base Form II.

FIG. 6 is a thermal characterization for free base Form II.

FIG. 7 is a XRPD profile for free base Material N.

FIG. 8 is a thermal characterization for free base Material N.

FIG. 9 depicts an Energy-Temperature Diagram between the Free Base Forms I, II, and Material N. The enthalpy (*H*) and free energy (G) isobars for each form are depicted as a function of temperature. ΔH_f is the heat of fusion; *T* is transition temperature; *m* is melt temperature; superscripts *I*, *II,* and *N* refer to the polymorphs. *Under the test conditions, not enough information was available to graphically represent the free energy isobar of Form I below 6 °C and above the estimated transition temperature $T^{N\text{-}II}$; the isobar likely intersects G_L at a temperature below m^{II}, allowing the possibility that Form I may be enantiotropic with Form II (where $T^{I\text{-}II}$ occurs below 6 °C) and/or Material N (where either $T^{I\text{-}N}$ occurs below $T^{I\text{-}II}$ or $T^{N\text{-}I}$ occurs above $T^{N\text{-}II}$, but not both). Free energy isobars can only intersect each other once.

FIG. 10 depicts ^{13}C Solid State NMR spectra for Free Base Forms I (bottom), II (middle), and Material N (top). Form I contains one molecule per asymmetric unit. Material N contains four molecules per asymmetric unit. As observed by ^{13}C Solid State NMR spectra, Forms II and N did not undergo a transition over 250 K to 340 K. Chemical shifts change slightly with temperature (not illustrated graphically).

FIG. 11 depicts ^{15}N Solid State NMR spectra for Free Base Forms I (bottom), II (middle), and Material N (top).

FIG. 12 depicts a differential scanning calorimetry (DSC) curve for Free Base Material N.

FIG. 13 depicts a DSC curve for Free Base Form II.

FIG. 14 depicts a DSC curve for Free Base Form I.

FIG. 15 depicts a XRPD profile of maturation experiments for the free base of Compound 1 at multiple temperatures.

FIG. 16 depicts a contemplated XRPD profile for solvated Material E.

FIG. 17 depicts a contemplated XRPD profile for solvated Material F.

FIG. 18 depicts a contemplated XRPD profile for solvated Material G.

FIG. 19 depicts a contemplated XRPD profile for solvated Material H.

FIG. 20 depicts a contemplated XRPD profile for solvated Material J.

FIG. 21 depicts a contemplated XRPD profile for solvated Material K.

FIG. 22 depicts a contemplated XRPD profile for solvated Material L.

FIG. 23 depicts a contemplated XRPD profile for solvated Material M.

FIG. 24 depicts a contemplated XRPD profile for solvated Material O.

FIG. 25 depicts an XRPD profile comparison of contemplated isostructural solvates of the free base of Compound 1. From top to bottom: Material E from acetone; Material F from ACN; Material G from DCM; Material H from dioxane; Material J from EtOH; Material K from IPA/water (also obtained from IPA); and Material L from THF, Material M from MEK.

Detailed Description

[0039] As noted above, this invention is directed to the stable free base Form II of Compound 1. However, prior to discussing this invention in further detail, the following terms will be defined.

Definitions

[0040] As used herein, the following terms have the following meanings.

[0041] The singular forms "a," "an," and "the" and the like include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes both a single compound and a plurality of different compounds.

[0042] The term "about" when used before a numerical designation, e.g., temperature, time, amount, and concentration, including a range, indicates approximations which may vary by ±10 %, ±5 % or ±1 %.

[0043] "Administration" refers to introducing an agent into a patient. A therapeutic amount can be administered, which can be determined by the treating physician or the like. An oral route of administration is preferred. The related terms and phrases administering" and "administration of", when used in connection with a compound or pharmaceutical composition (and grammatical equivalents) refer both to direct administration, which may be administration to a patient by a medical professional or by self-administration by the patient, and/or to indirect administration, which may be the act of prescribing a drug. For example, a physician who instructs a patient to self-administer a drug and/or provides a patient with a prescription for a drug is administering the drug to the patient. In any event, administration entails delivery to the patient of the drug.

[0044] The "crystalline ansolvate" of Compound 1 is a crystalline solid form of the free base of 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde, such as, e.g., crystalline Form I, Form II or Material N as disclosed herein. Each of the Form I, Form II or Material N crystal lattices is substantially free of solvents of crystallization. However, any solvent present is not included in the crystal lattice and is randomly distributed outside the crystal lattice. Therefore, Form I, Form II or Material N crystals in bulk may contain, outside the crystal lattice, small amounts of one or more solvents, such as the solvents used in its synthesis or crystallization. As used above, "substantially free of" and "small amounts," refers to the presence of solvents preferably less that 10,000 parts per million (ppm), or more preferably, less than 500 ppm.

[0045] The "crystalline solvate" of Compound 1 is a crystalline solid form of the free base of 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde, where the crystal lattices comprises one or more solvents of crystallization.

[0046] "Characterization" refers to obtaining data which may be used to identify a solid form of a compound, for example, to identify whether the solid form is amorphous or crystalline and whether it is unsolvated or solvated. The process by which solid forms are characterized involves analyzing data collected on the polymorphic forms so as to allow one of ordinary skill in the art to distinguish one solid form from other solid forms containing the same material. Chemical identity of solid forms can often be determined with solution-state techniques such as ^{13}C NMR or ^{1}H NMR. While these may help identify a material, and a solvent molecule for a solvate, such solution-state techniques themselves may not provide information about the solid state. There are, however, solid-state analytical techniques that can be used

to provide information about solid-state structure and differentiate among polymorphic solid forms, such as single crystal X-ray diffraction, X-ray powder diffraction (XRPD), solid state nuclear magnetic resonance (SS-NMR), and infrared and Raman spectroscopy, and thermal techniques such as differential scanning calorimetry (DSC), Solid state ^{13}C-NMR, thermogravimetry (TG), melting point, and hot stage microscopy.

[0047] To "characterize" a solid form of a compound, one may, for example, collect XRPD data on solid forms of the compound and compare the XRPD peaks of the forms. For example, when only three solid forms, e.g., Forms I and II and Material N, are compared and the Form I pattern shows a peak at an angle where no peaks appear in the Form II or Material N pattern, then that peak, for that compound, distinguishes Form I from Form II and Material N and further acts to characterize Form I. The collection of peaks which distinguish e.g., Form I from the other known forms is a collection of peaks which may be used to characterize Form I. Those of ordinary skill in the art will recognize that there are often multiple ways, including multiple ways using the same analytical technique, to characterize solid forms. Additional peaks could also be used, but are not necessary, to characterize the form up to and including an entire diffraction pattern. Although all the peaks within an entire XRPD pattern may be used to characterize such a form, a subset of that data may, and typically is, used to characterize the form.

[0048] An XRPD pattern is an x-y graph with diffraction angle (typically ° 2θ) on the x-axis and intensity on the y-axis. The peaks within this pattern may be used to characterize a crystalline solid form. As with any data measurement, there is variability in XRPD data. The data are often represented solely by the diffraction angle of the peaks rather than including the intensity of the peaks because peak intensity can be particularly sensitive to sample preparation (for example, particle size, moisture content, solvent content, and preferred orientation effects influence the sensitivity), so samples of the same material prepared under different conditions may yield slightly different patterns; this variability is usually greater than the variability in diffraction angles. Diffraction angle variability may also be sensitive to sample preparation. Other sources of variability come from instrument parameters and processing of the raw X-ray data: different X-ray instruments operate using different parameters and these may lead to slightly different XRPD patterns from the same solid form, and similarly different software packages process X-ray data differently and this also leads to variability. These and other sources of variability are known to those of ordinary skill in the pharmaceutical arts. Due to such sources of variability, it is usual to assign a variability of ±0.2° 2θ to diffraction angles in XRPD patterns.

[0049] "Comprising" or "comprises" is intended to mean that the compositions and methods include the recited elements, but not exclude others. "Consisting essentially of" when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination for the stated purpose. Thus, a composition consisting essentially of the elements as defined herein would not exclude other materials or steps that do not materially affect the basic and novel characteristic(s) of the claimed invention. "Consisting of" shall mean excluding more than trace elements of other ingredients and substantial method steps.

[0050] Form II and Material N are enantiotropic at a transition temperature (of approximately 42 °C). Below this transition temperature, Material N of the free base of Compound 1 is the thermodynamically more stable form relative to Forms I and II. Above this transition temperature, Form II of the free base of Compound 1 is the thermodynamically more stable form relative to Form I and Material N.

[0051] "Room temperature" refers to (22±5) °C.

[0052] "Therapeutically effective amount" or "therapeutic amount" refers to an amount of a drug or an agent that when administered to a patient suffering from a condition, will have the intended therapeutic effect, e.g., alleviation, amelioration, palliation or elimination of one or more manifestations of the condition in the patient. The therapeutically effective amount will vary depending upon the subject and the condition being treated, the weight and age of the subject, the severity of the condition, the particular composition or excipient chosen, the dosing regimen to be followed, timing of administration, the manner of administration and the like, all of which can be determined readily by one of ordinary skill in the art. The full therapeutic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations. For example, and without limitation, a therapeutically effective amount of an agent, in the context of treating disorders related to hemoglobin S, refers to an amount of the agent that alleviates, ameliorates, palliates, or eliminates one or more manifestations of the disorders related to hemoglobin S in the patient.

[0053] "Treatment", "treating", and "treat" are defined as acting upon a disease, disorder, or condition with an agent to reduce or ameliorate the harmful or any other undesired effects of the disease, disorder, or condition and/or its symptoms. Treatment, as used herein, covers the treatment of a human patient, and includes: (a) reducing the risk of occurrence of the condition in a patient determined to be predisposed to the disease but not yet diagnosed as having the condition, (b) impeding the development of the condition, and/or (c) relieving the condition, *i.e.,* causing regression of the condition and/or relieving one or more symptoms of the condition. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, multilineage hematologic improvement, decrease in the number of required blood transfusions, decrease in infections, decreased bleeding, and the like.

Identifying Forms I, II and Material N

[0054] When the HCl salt of Compound 1 was subjected to various stress conditions, disproportionation of the HCl salt in water was observed to generate the free base. At least three anhydrous crystalline forms of the free base were identified, termed Free Base Forms I, II, and Material N. It was discovered that nucleation of Free Base Form I generally occurs first and that extending the slurry time induces the transformation of Free Base Form I to Free Base Form II, a more thermodynamically stable phase relative to Form I. It was further discovered that Free Base Material N appears to be most stable form, relative to Forms I and II, at room temperature. Free Base Material N was found to be enantiotropically active relative to Form II, and will transform reversibly at a specific transition temperature (estimated herein near 42 °C). Above the transition temperature, Free Base Form II appears to be the most stable form, relative to Form I and Material N.

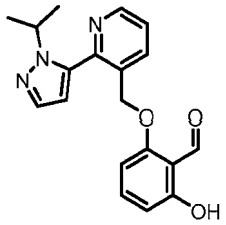
[0055] Based in part on solid-state nuclear magnetic resonance data, all three forms are crystalline and are distinct polymorphic forms. See FIGS 10 and 11. Form I contains one molecule per asymmetric unit, Form II contains two molecules per asymmetric unit and Form N contains four molecules per asymmetric unit. See the ^{15}N spectra in FIG. 11.

Ansolvates of Forms I, II and Material N

[0056] This invention provides the free base crystalline ansolvate of Compound 1, wherein the free base crystalline ansolvate is Form II. The free base crystalline ansolvate of Compound 1 may include one or more of Form I, Form II and/or Material N polymorphs. Preferably, the free base crystalline ansolvate of Compound 1 may include Form II and/or Material N polymorphs. More preferably, the free base crystalline ansolvate of Compound 1 may include the Material N polymorph. Yet more preferably, the free base crystalline ansolvate of Compound 1 is substantially free of a solvated polymorph of Compound 1 free base. Further yet more preferably, the free base crystalline ansolvate of Compound 1 is substantially free of other ansolvate polymorphs of Compound 1 free base. "Substantially free" of a component as used herein refers to contain up to about 5%, more preferably about 3%, and still more preferably about 1% of that component. As used herein, solvate includes a hydrate form as well.

Solvates of Compound 1

[0057] In one aspect, provided is a crystalline solvate of Compound 1:



Compound 1

[0058] In some embodiments, the crystalline solvate is substantially free of an ansolvated polymorph of Compound 1.

[0059] Many of the solubility and screen experiments with the free base of Compound 1 resulted in precipitation of solids characterized as solvate formation with some solvents. Under the conditions, solvates were not observed from the free base of Compound 1 with four solvents, including heptane, di-isopropyl ether (IPE), tert-methyl butyl ether (MTBE) and toluene. Solvates were observed from the free base of Compound 1 in nine solvents including acetone (Material E), acetonitrile (Material F), dichloromethane (Material G), dioxane (Material H), ethanol (Material J), isopropyl alcohol or a mixture of water and isopropyl alcohol (Material K), tetrahydrofuran (Material L), methyl ethyl ketone "MEK" (Material M), ethyl acetate (Material O) and dimethyl sulfoxide "DMSO" (Material P). The majority of the solvates (i.e., Materials E-H, J-M, O and P are contemplated to be isostructural. In some embodiments, the crystalline solvate includes one or more of Material E, Material F, Material G, Material H, Material J, Material K, Material L, Material M, Material O or Material P.

[0060] Material E can be characterized by at least one X-ray powder diffraction peak (Cu Kα radiation) selected from 8.69, 11.73, 12.10, 15.26, 16.11, 17.45, 22.39, 22.55 and 23.70 $\pm$ 0.20. Material F can be characterized by at least one X-ray powder diffraction peak (Cu Kα radiation) selected from 8.47, 8.81, 12.75, 13.17, 14.92, 15.63, 17.01 23.73, and 24.07 $\pm$ 0.20. Material G can be characterized by at least one X-ray powder diffraction peak (Cu Kα radiation) selected from 8.47, 11.45, 12.62, 14.66, 15.69, 17.01, 18.47, 20.32, 22.61, 23.08, 23.43 and 23.70 $\pm$ 0.20. Material H can be characterized by at least one X-ray powder diffraction peak (Cu Kα radiation) selected from 8.61, 11.67, 15.33, 16.28,

17.28, 22.58, 23.51 and 25.77 ± 0.20. Material J can be characterized by at least one X-ray powder diffraction peak (Cu Kα radiation) selected from 8.52, 8.88, 12.79, 15.04, 15.61, 17.11, 22.81, 23.87, 24.17, 24.62 and 26.44 ± 0.20. Material K can be characterized by at least one X-ray powder diffraction peak (Cu Kα radiation) selected from 8.52; 8.83, 11.35, 15.04, 15.74, 17.11, 23.46, 23.58, 24.08 and 25.99 ± 0.20. Material L can be characterized by at least one X-ray powder diffraction peak (Cu Kα radiation) selected from 8.61, 8.78, 11.67, 14.94, 15.28, 16.14, 17.30, 22.75, 23.71 and 26.05 ± 0.20; and Material M can be characterized by at least one X-ray powder diffraction peak (Cu Kα radiation) selected from 7.74, 10.05, 12.82, 15.33, 16.80, 20.82, 21.14, 25.80 and 26.97 ± 0.20.

[0061] The solvates (such as, of acetone, acetonitrile, dichloromethane, dioxane, ethanol, ethyl acetate, isopropyl alcohol, MEK, tetrahydrofuran or DMSO) could be used e.g., as intermediates to regenerate the free base crystalline ansolvate of Compound 1 by several methods including subjecting the solvate to vacuum conditions; and/or regenerating the HCl salt and disproportionating HCl; and/or washing the solvate with a solvent less prone to solvate formation such as heptane, di-isopropyl ether (IPE), tert-methyl butyl ether (MTBE) and toluene.

Table 1. Data Related to Solvates of the Free Base of Compound 1

Identifier	Crystallization Solvent	Volume (Å^3/Cell)	Number of Formula Units per Cell	Estimated Volume per Formula Unit* (Å^3)	Indexing Result
Material E	acetone	968	2	484	FIG 1
Material F	ACN	947	2	473	FIG 2
Material G	DCM	959	2	480	FIG 3
Material H	dioxane	977	2	488	FIG 4
Material J	EtOH	943	2	472	FIG 5
Material K	IPA	963	2	481	FIG 6
Material L	THF	972	2	486	FIG 7
Material M	MEK	3956	8	494	FIG 8
Material O	EtOAc	-	-	-	FIG 9
Material P**	DMSO	-	-	-	-
* The value is obtained by dividing the volume of the cell, derived from the tentative indexing solution, by the number of formula units within the cell. ** Material P was observed as a mixture with a "sulfate form I".					

[0062] Certain contemplated peaks of the various solvates provided herein are tabulated below. Certain peaks, which are preferably non-overlapping, low-angle peaks, with strong intensity, were not identified. The peaks were determined to the extent that the state of preferred orientation in the samples were unknown.

Table 2. Observed peaks for Material E.

°2θ	*d* space (Å)	Intensity (%)
8.41 ± 0.20	10.517 ± 0.256	13
8.69 ± 0.20	10.174 ± 0.239	100
11.73 ± 0.20	7.543 ± 0.130	17
12.10 ± 0.20	7.314 ± 0.122	20
13.00 ± 0.20	6.809 ± 0.106	15
14.02 ± 0.20	6.316 ± 0.091	5
14.77 ± 0.20	5.996 ± 0.082	16
15.26 ± 0.20	5.807 ± 0.077	34
15.81 ± 0.20	5.605 ± 0.071	7
16.11 ± 0.20	5.501 ± 0.069	20
16.48 ± 0.20	5.379 ± 0.066	11
16.65 ± 0.20	5.326 ± 0.064	11
16.88 ± 0.20	5.253 ± 0.063	3
17.26 ± 0.20	5.136 ± 0.060	9

(continued)

°2θ	*d* space (Å)	Intensity (%)
17.45 ± 0.20	5.083 ± 0.058	32
20.02 ± 0.20	4.435 ± 0.044	2
20.92 ± 0.20	4.246 ± 0.041	13
21.91 ± 0.20	4.057 ± 0.037	20
22.39 ± 0.20	3.970 ± 0.035	49
22.55 ± 0.20	3.944 ± 0.035	37
22.81 ± 0.20	3.898 ± 0.034	16
23.36 ± 0.20	3.807 ± 0.032	12
23.70 ± 0.20	3.755 ± 0.032	61
24.37 ± 0.20	3.653 ± 0.030	12
24.85 ± 0.20	3.583 ± 0.029	5
25.42 ± 0.20	3.504 ± 0.027	2
25.89 ± 0.20	3.442 ± 0.026	8
26.19 ± 0.20	3.403 ± 0.026	40
26.97 ± 0.20	3.306 ± 0.024	3
27.61 ± 0.20	3.231 ± 0.023	16
28.24 ± 0.20	3.160 ± 0.022	2
28.48 ± 0.20	3.134 ± 0.022	5
28.69 ± 0.20	3.111 ± 0.021	7
29.83 ± 0.20	2.995 ± 0.020	4

Table 3. Observed peaks for Material F.

°2θ	*d* space (Å)	Intensity (%)
8.47 ± 0.20	10.434 ± 0.252	100
8.81 ± 0.20	10.039 ± 0.233	49
11.42 ± 0.20	7.752 ± 0.138	15
12.75 ± 0.20	6.942 ± 0.110	27
13.17 ± 0.20	6.723 ± 0.103	21
13.87 ± 0.20	6.384 ± 0.093	7
14.61 ± 0.20	6.064 ± 0.084	13
14.92 ± 0.20	5.936 ± 0.080	43
15.51 ± 0.20	5.713 ± 0.074	24
15.63 ± 0.20	5.671 ± 0.073	43
15.96 ± 0.20	5.553 ± 0.070	15
17.01 ± 0.20	5.212 ± 0.062	31
17.26 ± 0.20	5.136 ± 0.060	4
17.70 ± 0.20	5.011 ± 0.057	9
18.17 ± 0.20	4.883 ± 0.054	4
18.79 ± 0.20	4.724 ± 0.050	10
19.35 ± 0.20	4.587 ± 0.047	4
19.49 ± 0.20	4.555 ± 0.047	3
20.02 ± 0.20	4.435 ± 0.044	4
20.29 ± 0.20	4.377 ± 0.043	9
21.06 ± 0.20	4.219 ± 0.040	11
21.33 ± 0.20	4.167 ± 0.039	4
22.71 ± 0.20	3.915 ± 0.034	27
23.11 ± 0.20	3.848 ± 0.033	15
23.73 ± 0.20	3.749 ± 0.031	42
24.07 ± 0.20	3.698 ± 0.031	59

(continued)

°2θ	*d* space (Å)	Intensity (%)
24.65 ± 0.20	3.612 ± 0.029	87
24.95 ± 0.20	3.569 ± 0.028	6
25.20 ± 0.20	3.534 ± 0.028	5
25.69 ± 0.20	3.468 ± 0.027	15
26.52 ± 0.20	3.361 ± 0.025	61
26.79 ± 0.20	3.328 ± 0.025	10
27.02 ± 0.20	3.300 ± 0.024	9

Table 4. Observed peaks for Material G.

°2θ	*d* space (Å)	Intensity (%)
8.47 ± 0.20	10.434 ± 0.252	45
8.76 ± 0.20	10.096 ± 0.235	12
11.45 ± 0.20	7.729 ± 0.137	76
12.62 ± 0.20	7.015 ± 0.113	36
13.09 ± 0.20	6.765 ± 0.105	10
13.87 ± 0.20	6.384 ± 0.093	5
14.66 ± 0.20	6.044 ± 0.083	39
14.92 ± 0.20	5.936 ± 0.080	26
15.33 ± 0.20	5.782 ± 0.076	7
15.69 ± 0.20	5.647 ± 0.072	88
16.01 ± 0.20	5.536 ± 0.070	8
16.76 ± 0.20	5.289 ± 0.063	15
17.01 ± 0.20	5.212 ± 0.062	29
17.50 ± 0.20	5.068 ± 0.058	5
17.60 ± 0.20	5.040 ± 0.057	4
18.13 ± 0.20	4.892 ± 0.054	5
18.47 ± 0.20	4.804 ± 0.052	21
19.55 ± 0.20	4.540 ± 0.046	4
20.01 ± 0.20	4.439 ± 0.044	5
20.32 ± 0.20	4.370 ± 0.043	20
21.11 ± 0.20	4.209 ± 0.040	15
22.61 ± 0.20	3.932 ± 0.035	42
22.88 ± 0.20	3.887 ± 0.034	9
23.08 ± 0.20	3.854 ± 0.033	28
23.43 ± 0.20	3.797 ± 0.032	56
23.70 ± 0.20	3.755 ± 0.032	48
24.12 ± 0.20	3.690 ± 0.030	13
24.42 ± 0.20	3.646 ± 0.030	100
25.05 ± 0.20	3.555 ± 0.028	7
25.40 ± 0.20	3.506 ± 0.027	26
26.36 ± 0.20	3.382 ± 0.025	50
26.57 ± 0.20	3.355 ± 0.025	7
26.82 ± 0.20	3.324 ± 0.025	27
27.07 ± 0.20	3.294 ± 0.024	10

Table 5. Observed peaks for Material H.

°2θ	*d* space (Å)	Intensity (%)
8.61 ± 0.20	10.273 ± 0.244	48

(continued)

°2θ	*d* space (Å)	Intensity (%)
8.81 ± 0.20	10.039 ± 0.233	20
11.67 ± 0.20	7.586 ± 0.132	32
12.10 ± 0.20	7.314 ± 0.122	11
12.79 ± 0.20	6.924 ± 0.110	9
14.56 ± 0.20	6.085 ± 0.084	4
14.87 ± 0.20	5.956 ± 0.081	22
15.33 ± 0.20	5.782 ± 0.076	42
15.76 ± 0.20	5.623 ± 0.072	18
16.28 ± 0.20	5.445 ± 0.067	51
16.73 ± 0.20	5.299 ± 0.064	9
17.28 ± 0.20	5.132 ± 0.060	61
17.68 ± 0.20	5.016 ± 0.057	3
20.47 ± 0.20	4.338 ± 0.042	12
21.38 ± 0.20	4.157 ± 0.039	7
21.83 ± 0.20	4.072 ± 0.037	4
22.23 ± 0.20	3.999 ± 0.036	9
22.58 ± 0.20	3.938 ± 0.035	100
22.95 ± 0.20	3.876 ± 0.034	6
23.11 ± 0.20	3.848 ± 0.033	14
23.51 ± 0.20	3.783 ± 0.032	88
24.37 ± 0.20	3.653 ± 0.030	13
24.65 ± 0.20	3.612 ± 0.029	10
25.77 ± 0.20	3.457 ± 0.027	41
26.67 ± 0.20	3.342 ± 0.025	7
26.97 ± 0.20	3.306 ± 0.024	5
27.66 ± 0.20	3.225 ± 0.023	3
28.11 ± 0.20	3.174 ± 0.022	4
28.61 ± 0.20	3.120 ± 0.022	6
28.96 ± 0.20	3.083 ± 0.021	4
29.23 ± 0.20	3.055 ± 0.021	3
29.63 ± 0.20	3.015 ± 0.020	3

Table 6. Observed peaks for Material J.

°2θ	*d* space (Å)	Intensity (%)
8.52 ± 0.20	10.373 ± 0.249	100
8.88 ± 0.20	9.964 ± 0.229	39
11.33 ± 0.20	7.809 ± 0.140	22
12.79 ± 0.20	6.924 ± 0.110	25
13.12 ± 0.20	6.748 ± 0.104	24
13.94 ± 0.20	6.354 ± 0.092	4
14.47 ± 0.20	6.120 ± 0.085	14
15.04 ± 0.20	5.890 ± 0.079	42
15.61 ± 0.20	5.677 ± 0.073	56
15.84 ± 0.20	5.594 ± 0.071	16
17.11 ± 0.20	5.181 ± 0.061	33
17.40 ± 0.20	5.097 ± 0.059	4
17.82 ± 0.20	4.979 ± 0.056	8
18.12 ± 0.20	4.897 ± 0.054	3
18.90 ± 0.20	4.695 ± 0.050	11

(continued)

°2θ	*d* space (Å)	Intensity (%)
19.39 ± 0.20	4.579 ± 0.047	5
19.62 ± 0.20	4.525 ± 0.046	4
20.16 ± 0.20	4.406 ± 0.044	8
20.96 ± 0.20	4.239 ± 0.040	12
22.81 ±0.20	3.898 ± 0.034	27
23.15 ± 0.20	3.843 ± 0.033	9
23.28 ± 0.20	3.821 ± 0.033	7
23.87 ± 0.20	3.729 ± 0.031	34
24.17 ± 0.20	3.683 ± 0.030	52
24.62 ± 0.20	3.616 ± 0.029	95
25.20 ± 0.20	3.534 ± 0.028	5
25.77 ± 0.20	3.457 ± 0.027	13
26.44 ± 0.20	3.371 ± 0.025	70
26.71 ± 0.20	3.338 ± 0.025	10
27.21 ± 0.20	3.278 ± 0.024	7

Table 7. Observed peaks for GBT000440, Material K.

°2θ	*d* space (Å)	Intensity (%)
8.52 ± 0.20	10.373 ± 0.249	75
8.83 ± 0.20	10.020 ± 0.232	33
11.35 ± 0.20	7.797 ± 0.139	29
12.52 ± 0.20	7.071 ± 0.114	21
12.90 ± 0.20	6.861 ± 0.108	24
13.92 ± 0.20	6.361 ± 0.092	4
14.49 ± 0.20	6.113 ± 0.085	18
15.04 ± 0.20	5.890 ± 0.079	41
15.34 ± 0.20	5.775 ± 0.076	17
15.74 ± 0.20	5.629 ± 0.072	57
15.93 ± 0.20	5.564 ± 0.070	13
16.61 ± 0.20	5.336 ± 0.065	7
17.11 ± 0.20	5.181 ± 0.061	33
17.70 ± 0.20	5.011 ± 0.057	7
18.00 ± 0.20	4.928 ± 0.055	4
18.38 ± 0.20	4.826 ± 0.053	13
19.04 ± 0.20	4.662 ± 0.049	4
19.74 ± 0.20	4.498 ± 0.046	5
20.21 ± 0.20	4.395 ± 0.043	11
20.99 ± 0.20	4.232 ± 0.040	12
22.70 ± 0.20	3.918 ± 0.034	22
22.90 ± 0.20	3.884 ± 0.034	17
23.46 ± 0.20	3.791 ± 0.032	45
23.58 ± 0.20	3.773 ± 0.032	70
24.08 ± 0.20	3.695 ± 0.030	100
24.75 ± 0.20	3.597 ± 0.029	6
25.19 ± 0.20	3.536 ± 0.028	21
25.99 ± 0.20	3.429 ± 0.026	71
26.71 ± 0.20	3.338 ± 0.025	11
27.36 ± 0.20	3.260 ± 0.024	9
28.11 ± 0.20	3.174 ± 0.022	4

(continued)

°2θ	*d* space (Å)	Intensity (%)
28.69 ± 0.20	3.111 ± 0.021	9

Table 8. Observed peaks for Material L.

°2θ	*d* space (Å)	Intensity (%)
8.61 ± 0.20	10.273 ± 0.244	79
8.78 ± 0.20	10.077 ± 0.235	38
11.67 ± 0.20	7.586 ± 0.132	35
12.17 ±0.20	7.274 ±0.121	19
12.94 ± 0.20	6.844 ± 0.107	14
14.07 ± 0.20	6.293 ± 0.090	3
14.62 ± 0.20	6.057 ± 0.084	5
14.94 ± 0.20	5.929 ± 0.080	25
15.28 ± 0.20	5.800 ± 0.076	50
15.93 ± 0.20	5.564 ± 0.070	18
16.14 ± 0.20	5.490 ± 0.068	49
16.33 ± 0.20	5.429 ± 0.067	9
16.70 ± 0.20	5.310 ± 0.064	9
16.85 ± 0.20	5.263 ± 0.063	6
17.30 ± 0.20	5.127 ± 0.060	52
17.63 ± 0.20	5.030 ± 0.057	6
18.37 ± 0.20	4.830 ± 0.053	3
20.14 ± 0.20	4.409 ± 0.044	5
20.59 ± 0.20	4.314 ± 0.042	14
21.53 ± 0.20	4.128 ± 0.038	11
22.01 ± 0.20	4.038 ± 0.037	3
22.44 ± 0.20	3.961 ± 0.035	27
22.75 ± 0.20	3.910 ± 0.034	72
23.10 ± 0.20	3.851 ± 0.033	20
23.31 ± 0.20	3.816 ± 0.033	19
23.48 ± 0.20	3.789 ± 0.032	12
23.71 ± 0.20	3.752 ± 0.031	100
24.48 ± 0.20	3.636 ± 0.029	20
24.70 ± 0.20	3.604 ± 0.029	4
24.93 ± 0.20	3.571 ± 0.028	3
25.59 ± 0.20	3.482 ± 0.027	5
25.72 ± 0.20	3.464 ± 0.027	5
26.05 ± 0.20	3.420 ± 0.026	62
26.59 ± 0.20	3.352 ± 0.025	6
27.14 ± 0.20	3.286 ± 0.024	8
27.83 ± 0.20	3.206 ± 0.023	8
28.38 ± 0.20	3.145 ± 0.022	3
28.78 ± 0.20	3.102 ± 0.021	8
29.05 ± 0.20	3.074 ± 0.021	4
29.36 ± 0.20	3.042 ± 0.020	3

Table 9. Observed peaks for Material M.

°2θ	*d* space (Å)	Intensity (%)
7.74 ± 0.20	11.424 ± 0.303	100

(continued)

°2θ	*d* space (Å)	Intensity (%)
8.34 ± 0.20	10.601 ± 0.260	4
10.05 ±0.20	8.806 ± 0.178	17
12.82 ± 0.20	6.906 ± 0.109	46
13.05 ± 0.20	6.783 ± 0.105	4
14.17 ± 0.20	6.249 ± 0.089	2
14.54 ± 0.20	6.092 ± 0.085	6
14.99 ± 0.20	5.910 ± 0.079	16
15.33 ±0.20	5.782 ± 0.076	47
15.53 ± 0.20	5.707 ± 0.074	21
16.80 ± 0.20	5.278 ± 0.063	27
18.33 ± 0.20	4.839 ± 0.053	3
19.17 ± 0.20	4.630 ± 0.048	22
20.19 ± 0.20	4.399 ± 0.044	23
20.82 ± 0.20	4.266 ± 0.041	32
21.14 ± 0.20	4.202 ± 0.040	27
21.29 ± 0.20	4.173 ± 0.039	14
22.01 ±0.20	4.038 ± 0.037	13
22.28 ± 0.20	3.991 ± 0.036	23
22.93 ± 0.20	3.879 ± 0.034	6
23.35 ± 0.20	3.810 ± 0.032	11
24.00 ± 0.20	3.708 ± 0.031	14
24.25 ± 0.20	3.670 ± 0.030	3
24.88 ± 0.20	3.578 ± 0.029	11
25.54 ± 0.20	3.488 ± 0.027	9
25.80 ± 0.20	3.453 ± 0.027	94
26.97 ± 0.20	3.306 ± 0.024	27
27.63 ± 0.20	3.229 ± 0.023	2
28.41 ±0.20	3.142 ± 0.022	7
28.54 ± 0.20	3.127 ± 0.022	8
29.03 ± 0.20	3.076 ± 0.021	3
29.30 ± 0.20	3.049 ± 0.020	7
29.63 ± 0.20	3.015 ± 0.020	15

Pharmaceutical Compositions

[0063] In another of its composition embodiments, this invention provides for a pharmaceutical composition comprising a pharmaceutically acceptable excipient and crystalline free base ansolvate of Compound 1, including the Form II polymorph.

[0064] Such compositions can be formulated for different routes of administration. Although compositions suitable for oral delivery will probably be used most frequently, other routes that may be used include intravenous, intraarterial, pulmonary, rectal, nasal, vaginal, lingual, intramuscular, intraperitoneal, intracutaneous, intracranial, subcutaneous and transdermal routes. Suitable dosage forms for administering any of the compounds described herein include tablets, capsules, pills, powders, aerosols, suppositories, parenterals, and oral liquids, including suspensions, solutions and emulsions. Sustained release dosage forms may also be used, for example, in a transdermal patch form. All dosage forms may be prepared using methods that are standard in the art (see e.g., Remington's Pharmaceutical Sciences, 16th ed., A. Oslo editor, Easton Pa. 1980).

[0065] Pharmaceutically acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of this invention. Such excipients may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art. Pharmaceutical compositions in accordance with the invention are prepared by conventional means using methods known in the art.

[0066] The compositions disclosed herein may be used in conjunction with any of the vehicles and excipients commonly

employed in pharmaceutical preparations, e.g., talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous solvents, oils, paraffin derivatives, glycols, etc. Coloring and flavoring agents may also be added to preparations, particularly to those for oral administration. Solutions can be prepared using water or physiologically compatible organic solvents such as ethanol, 1,2-propylene glycol, polyglycols, dimethylsulfoxide, fatty alcohols, triglycerides, partial esters of glycerin and the like.

[0067] Solid pharmaceutical excipients include starch, cellulose, hydroxypropyl cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. In certain embodiments, the compositions provided herein comprises one or more of α-tocopherol, gum arabic, and/or hydroxypropyl cellulose.

[0068] In one embodiment, this invention provides sustained release formulations such as drug depots or patches comprising an effective amount of a compound provided herein. In another embodiment, the patch further comprises gum Arabic or hydroxypropyl cellulose separately or in combination, in the presence of alpha-tocopherol. Preferably, the hydroxypropyl cellulose has an average MW of from 10,000 to 100,000. In a more preferred embodiment, the hydroxypropyl cellulose has an average MW of from 5,000 to 50,000.

[0069] Compounds and pharmaceutical compositions of this invention maybe used alone or in combination with other compounds. When administered with another agent, the co-administration can be in any manner in which the pharmacological effects of both are manifest in the patient at the same time. Thus, co-administration does not require that a single pharmaceutical composition, the same dosage form, or even the same route of administration be used for administration of both the compound of this invention and the other agent or that the two agents be administered at precisely the same time. However, co-administration will be accomplished most conveniently by the same dosage form and the same route of administration, at substantially the same time. Obviously, such administration most advantageously proceeds by delivering both active ingredients simultaneously in a novel pharmaceutical composition in accordance with the present invention.

Preparative and Treatment Methods

Ansolvate

[0070] In another aspect, a method of preparing the crystalline free base ansolvate of Compound 1 is provided. In one embodiment, provided herein is a method of preparing the crystalline free base of Compound 1 comprising slurrying or contacting the HCl salt of the Compound 1 with water and allowing dissociation of HCl to produce the free base of Compound 1. In one embodiment, the crystalline free base ansolavte of Compound 1 prepared comprises one or more of Form I, Form II and Material N.

[0071] The crystalline Form II of the free base of Compound 1 of the claims can be used in methods for increasing oxygen affinity of hemoglobin S in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of the crystalline Form II of the free base of Compound 1 of the claims.

[0072] The crystalline Form II of the free base of Compound 1 of the claims can be used in methods for treating oxygen deficiency associated with sickle cell anemia in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of the crystalline Form II of the free base of Compound 1 of the claims.

[0073] The crystalline Form II of the free base of Compound 1 of the claims can be for use in a method of treating sickle cell disease, the method comprising administering to a subject in need thereof a therapeutically effective amount of the crystalline Form II of the free base of Compound 1 of the claims. The crystalline free base of Compound 1 is an ansolvate. The crystalline free base of Compound 1 is Form II. The crystalline Form II of the free base of Compound 1 of the claims can be for use in a method of treating cancer, a pulmonary disorder, stroke, high altitude sickness, an ulcer, a pressure sore, Alzheimer's disease, acute respiratory disease syndrome, and a wound, the method comprising administering to a subject in need thereof a therapeutically effective amount of the crystalline Form II of the free base of Compound 1 of the claims. The crystalline free base of Compound 1 is an ansolvate. The crystalline free base of Compound 1 is Form II.

[0074] In such treatments, the dosing of the crystalline Form II of the free base of Compound 1 of the claims to the treated patient is already disclosed in the art.

Solvates

[0075] In another aspect, a method of preparing the crystalline free base solvates of Compound 1 is provided. In some embodiments, a free base ansolvate, as described herein (e.g, as obtained by slurrying an HCl salt of Compound 1 in water) of Compound 1 is contacted with a solvent as provided herein, including a mixture of solvents, to prepare the

solvate. the solvent or the mixture of solvents. Thus, a solvent can be a single solvent or substantially a single solvent or a mixture of solvents. When a mixture of solvents is used, a solvate can be produced having one or more of the individual constituent solvents of the solvent mixture. In some embodiments, the solvent includes alcoholic solvents such as mono di or higher alcohols or alkanols. In some embodiments, the solvent includes chlorinated solvents such as dichloromethane chloroform, et cetera. In some embodiments, the solvent includes ketone solvents such as alkanones and cycloalkanones. Certain solvents include without limitation, methanol, ethanol, 2-propanol, 2-methyl-1-propanol, 1-butanol, acetonitrile, acetone, dichloromethane, dioxane, or tetrahydrofuran, or combinations thereof, optionally including water.

[0076] In another aspect, a method is provided for increasing oxygen affinity of hemoglobin S in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of a crystalline solvate of Compound 1.

[0077] In another aspect, a method is provided for treating oxygen deficiency associated with sickle cell anemia, the method comprising administering to a subject in need thereof a therapeutically effective amount of a crystalline solvate of Compound 1.

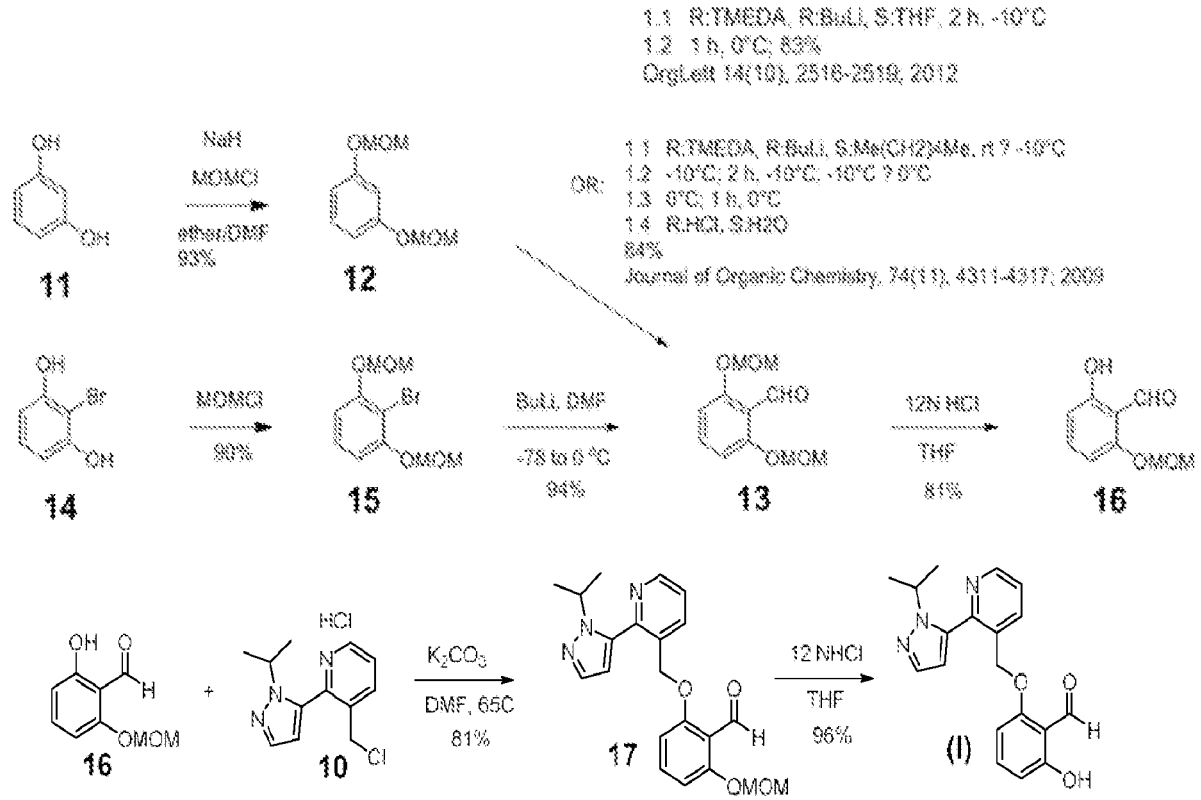
EXAMPLES

[0078] The following examples describe the preparation, characterization, and properties of the free base of Compound 1 Form I ansolvate. Unless otherwise stated, all temperatures are in degrees Celcius (°C) and the following abbreviations have the following definitions:

DSC	Differential scanning calorimetry
DVS	Dynamic vapor sorption
HPLC	High performance liquid chromatography
NA	Not applicable
ND	Not determined
Q	Percent dissolved per unit time
RH	Relative humidity
RSD	Residual standard deviation
RRT	Relative retention time
SS-NMR	Solid state nuclear magnetic resonance
TGA	Thermogravimetric analysis
TG-IR	Thermogravimetric infra red analysis
XRPD	X-ray powder diffraction
VT-XRPD	Variable temperature X-ray powder diffraction

Synthetic Routes for Preparing Compound 1

[0079] The compound of formula (I) was synthesized as schematically described below and elaborated thereafter.



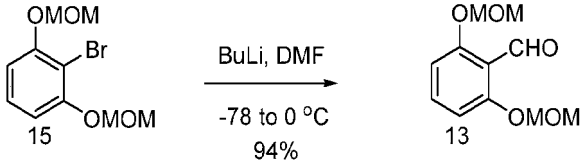
Example 1: Synthesis of Compound 15

[0080]

[0081] To a solution of 2-bromobenzene-1,3-diol (5 g, 26.45 mmol) in DCM (50 ml) at 0 °C was added DIPEA (11.54 mL, 66.13 mmol) and MOMCl (4.42 mL, 58.19 mmol). The mixture was stirred at 0 °C for 1.5 h, and then warmed to room temperature. The solution was diluted with DCM, washed with sat. $NaHCO_3$, brine, dried and concentrated to give crude product, which was purified by column (hexanes/EtOAc=4:1) to give desired product 15.58 g (90%).

Example 2: Synthesis of Compound 13 from 15

[0082]

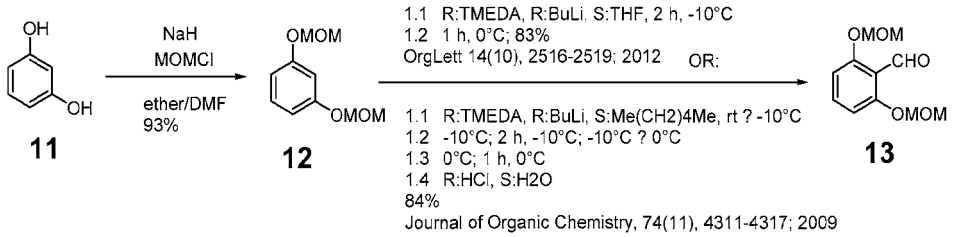


[0083] To a solution of 2-bromo-1,3-bis(methoxymethoxy)benzene (15) (19.9g, 71.8 mmol) in THF (150 mL) at -78 °C was added BuLi (2.5 M, 31.6 mL, 79.0 mmol) dropwise. The solution was stirred at -78 °C for 25 min (resulting white cloudy mixture), then it was warmed to 0 °C and stirred for 25 min. The reaction mixture slowly turns homogenous. To the solution was added DMF at 0 °C. After 25 min, HPLC showed reaction completed. The mixture was quenched with

sat. NH4Cl (150 mL), diluted with ether (300 mL). The organic layer was separated, aq layer was further extracted with ether (2X200 mL), and organic layer was combined, washed with brine, dried and concentrated to give crude product, which was triturated to give 14.6 g desired product. The filtrate was then concentrated and purified by column to give additional 0.7 g, total mass is 15.3 g.

Example 3: Synthesis of Compound 13 from resorcinol 11

[0084]



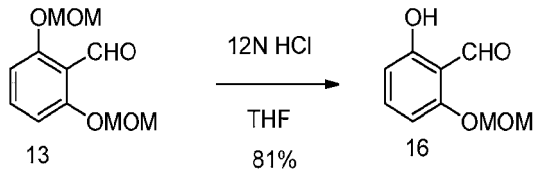
[0085] A three-necked round-bottom flask equipped with mechanical stirrer was charged with 0.22 mol of NaH (50 % suspension in mineral oil) under nitrogen atmosphere. NaH was washed with 2 portions (100 mL) of n-hexane and then with 300 mL of dry diethyl ether; then 80 mL of anhydrous DMF was added. Then 0.09 mol of resorcinol 11, dissolved in 100 mL of diethyl ether was added dropwise and the mixture was left under stirring at rt for 30 min. Then 0.18 mol of MOMCl was slowly added. After 1 h under stirring at rt, 250 mL of water was added and the organic layer was extracted with diethyl ether. The extracts were washed with brine, dried (Na_2SO_4), then concentrated to give the crude product that was purified by silica gel chromatography to give compound 12 (93 % yield).

[0086] A three-necked round-bottom flask was charged with 110 mL of n-hexane, 0.79 mol of BuLi and 9.4 mL of tetramethylethylendiamine (TMEDA) under nitrogen atmosphere. The mixture was cooled at -10 °C and 0.079 mol of bis-phenyl ether 12 was slowly added. The resulting mixture was left under magnetic stirring at -10 °C for 2 h. Then the temperature was raised to 0 °C and 0.067 mol of DMF was added dropwise. After 1 h, aqueous HCl was added until the pH was acidic; the mixture was then extracted with ethyl ether. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to give aldehyde **13** (84%).

[0087] 2,6-bis(methoxymethoxy)benzaldehyde (13): mp 58-59 °C (n-hexane) ; IR (KBr) n: 1685 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.51 (s, 6H, 2 OCH_3), 5.28 (s, 4H, 2 OCH_2O), 6.84 (d, 2H, J = 8.40 Hz, H-3, H-5), 7.41 (t, 1H, J = 8.40 Hz, H-4), 10.55 (s, 1H, CHO); MS, m/e (relative intensity) 226 (M+, 3), 180 (4), 164 (14), 122 (2), 92 (2), 45 (100); Anal. Calc'd. for $C_{11}H_{14}O_5$: C,58.40; H, 6.24. Found: C, 57.98; H, 6.20.

Example 4: The Synthesis of Compound 16

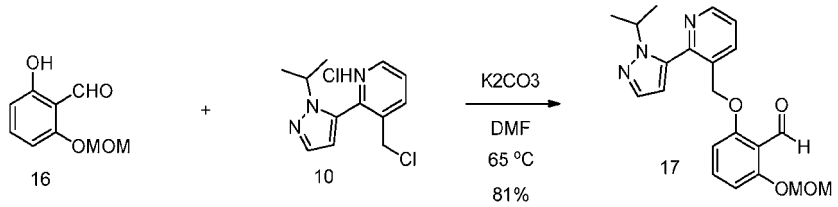
[0088]



[0089] To a solution of 2,6-bis(methoxymethoxy)benzaldehyde **(13)** (15.3 g, 67.6 mmol) in THF (105 mL) (solvent was purged with N_2) was added conc. HCl (12N, 7 mL) under N_2, then it was further stirred under N_2 for 1.5 h. To the solution was added brine (100 mL) and ether (150 ml). The organic layer was separated and the aqueous layer was further extracted with ether (2x200 mL). The organic layer was combined, washed with brine, dried and concentrated to give crude product, which was purified by column (300g, hexanes/EtOAc=85:15) to give desired product **16** (9.9 g) as yellow liquid.

Example 5: Synthesis of Compound 17

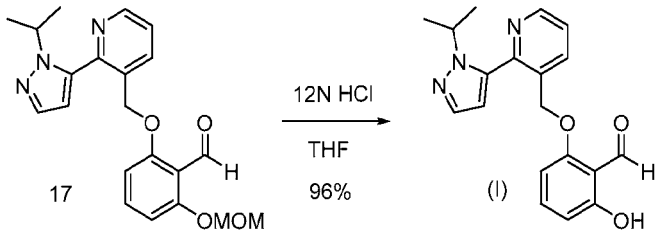
[0090]



[0091] To a solution of 2-hydroxy-6-(methoxymethoxy)benzaldehyde **(16)** (10.88 g, 59.72 mmol) in DMF (120 mL) (DMF solution was purged with N_2 for 10 min) was added K_2CO_3 (32.05 g, 231.92 mmol) and 3-(chloromethyl)-2-(1-isopropyl-1H-pyrazol-5-yl)pyridine hydrochloride **(10)** (15.78 g, 57.98 mmol). The mixture was heated at 65 °C for 1.5 h, cooled to rt, poured into ice water (800 mL). The precipitated solids were isolated by filtration, dried and concentrated to give desired product (**17,** 18 g).

Example 6: Synthesis of Compound (I)

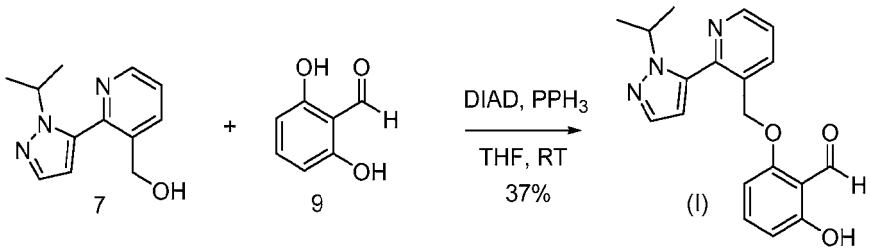
[0092]



[0093] To a solution of 2-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-(methoxymethoxy)benzaldehyde (17) (18 g, 47.19 mmol) in THF (135 mL, solution was purged with N_2) was added conc. HCl (12N, 20 mL). The solution was stirred at rt for 3 h when HPLC showed the reaction complete. The mixture was added to a solution of $NaHCO_3$ (15 g) in water (1.2 L), and the resulting precipitate was collected by filtration, dried to give crude solid, which was further purified by column (DCM/EtOAc=60:40) to give pure product (15.3 g).

Example 7: Synthesis of Compound I (free base) and its HCl salt form

[0094] Compound (I) free base (40g) was obtained from the coupling of the alcohol intermediate 7 and 2,6-dihydroxy-benzaldedhye 9 under Mitsunobu conditions. A procedure is also provided below:



Example 8: Synthesis of Compound (I) by Mitsunobu coupling

[0095] Into a 2000-mL three neck round-bottom flask, which was purged and maintained with an inert atmosphere of nitrogen, was placed a solution of [2-[1-(propan-2-yl)-1H-pyrazol-5-yl]pyridin-3-yl]methanol (7) (70 g, 322.18 mmol, 1.00 equiv) in tetrahydrofuran

[0096] (1000 mL). 2,6-Dihydroxybenzaldehyde (9) (49.2 g, 356.21 mmol, 1.10 equiv) and PPh_3 (101 g, 385.07 mmol, 1.20 equiv) were added to the reaction mixture. This was followed by the addition of a solution of DIAD (78.1 g, 386.23 mmol, 1.20 equiv) in tetrahydrofuran (200 ml) dropwise with stirring. The resulting solution was stirred overnight at room temperature. The resulting solution was diluted with 500 ml of H_2O. The resulting solution was extracted with 3x500 ml of dichloromethane and the combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with EA:PE (1:50-1:3) as eluent to yield the crude product. The crude

product was re-crystallized from i-propanol/H_2O in the ratio of 1/1.5. This resulted in 40 g (37%) of 2-hydroxy-6-([2-[1-(propan-2-yl)-1H-pyrazol-5-yl]pyridin-3-yl]methoxy)benzaldehyde as a light yellow solid. The compound exhibited a melting point of 80-82 °C. MS (ES, *m*/*z*): 338.1 [M+1]. ^{1}H NMR (300 MHz, DMSO-d6) δ 11.72(s, 1H), 10.21(s, 1H), 8.76(d, J=3.6Hz, 1H), 8.24(d, J=2.7Hz, 1H),7.55(m, 3H), 6.55(m,3H) ,5.21 (s, 2H), 4.65 (m, 1H), 1.37 (d, J=5.1Hz, 6H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 10.40 (s, 1H), 8.77 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.49 - 7.34 (m, 2H), 6.59 (d, *J* = 8.5 Hz, 1H), 6.37 (d, *J* = 1.8 Hz, 1H), 6.29 (d, *J* = 8.2 Hz, 1H), 5.10 (s, 2H), 4.67 (sep, *J* = 6.7 Hz, 1H), 1.50 (d, *J* = 6.6 Hz, 6H).

[0097] In another approach, multiple batches of Compound (I) free base are prepared in multi gram quantities (20g). The advantage of this route is the use of mono-protected 2,6-dihydroxybenzaldehyde **(16),** which effectively eliminates the possibility of bis-alkylation side product. The mono-MOM ether of 2,6-dihydroxybenzaldehyde **(16)** can be obtained from two starting points, bromoresorcinol **(14)** or resorcinol **(11)** [procedures described in the Journal of Organic Chemistry, 74(11), 4311-4317; 2009]. All steps and procedures are provided below. Due to the presence of phenolic aldehyde group, precautions (i.e., carry out all reactions under inert gas such as nitrogen) should be taken to avoid oxidation of the phenol and/or aldehyde group.

[0098] Preparation of compound I HCl salt: A solution of compound I (55.79 g, 165.55 mmol) in acetonitrile (275 mL) was flushed with nitrogen for 10 min, then to this solution was added 3N aqueous HCl (62 mL) at room temperature. The mixture was stirred for additional 10 min after the addition, most of the acetonitrile (about 200 mL) was then removed by evaporation on a rotary evaporator at around 32 °C, the remaining solution was frozen by cooling in an acetone-dry ice bath and lyophilized to afford compound I HCl salt (59.4 g).

Example 9: Characterization of the HCl salt of Compound 1

Technique	Details	Result
XRPD	indexed	HCl salt of Compound 1
Microscope	-	pale yellow solids, thin blades/tablets, birefringent
^{1}H NMR	DMSO-d6	consistent with structure, <0.01 moles MEK
XRPD	-	HCl salt of Compound 1
DVS	-	0.03% gain upon equilibration at 5% RH 0.10% gain from 5 to 95% RH 0.09% loss from 95 to 5%RH
	post XRPD	HCl I + Free Base Form I

Example 10: Physical Stability of the HCl salt of Compound 1 Exposed to Water

Condition	Time (all times are approximated)	Observation	XRPD Result
contacted w/ water	-	sheet formation after 5 min	-
water slurry	about 5 min	Floating yellow solids convert to white solids upon isolation	Free base (FB) I (indexed)
vacuum dried	about 1 day	Remain	FB I
water slurry	about 6 days	white, thin blades, birefringent (B)	FB I + FB II

Example 11: Physical Stability of the HCl salt of Compound 1 with Grinding

Condition	Time	Observation	XRPD Result
grinding, dry	30 min	off white/pale yellow	HCl I
grinding, wet	30 min	off white/pale yellow paste	HCl I + FB I

Example 12: Physical Stability of the HCl salt of Compound 1 Exposed to Elevated Temperature and/or Vacuum

Condition	Time	Observation	XRPD Result
RT vacuum	6 days	pale yellow, blades/plates, B	HCl I + FB I
30 °C	6 hrs	pale yellow, blades/tablets, B	HCl I
	12 hrs	pale yellow, blades/tablets, B	HCl I + FB I
	24 hrs	pale yellow, blades/tablets, B	HCl I + FB I
40 °C	6 hrs	pale yellow, blades/tablets, B	HCl I + FB I
	12 hrs	pale yellow, blades/tablets, B	HCl I + FB I
	24 hrs	pale yellow, blades/tablets, B	HCl I + FB I
40 °C vacuum	6 hrs	pale yellow, blades/tablets, B	HCl I + FB I
	12 hrs	pale yellow, blades/tablets, B	HCl I + FB I
	24 hrs	pale yellow, blades/tablets, B	HCl I + FB I
60 °C	6 days	pale yellow blades, B	HCl I + FB I
60 °C vacuum	6 days	pale yellow, blades, B; irregular residue	HCl I + FB I + other free base form
100 to 125 °C	20 min	pH paper above sample indicate acidic volatiles	HCl I + FB I + other free base form

Example 13: Generation of the Free Base of Compound 1 from the Disproportionation of the HCl salt of Compound 1 in Water (The starting material is the HCl salt of Compound 1).

Method	Observation	XRPD Result
1. contacted with water 2. sonicated 3. filtered and rinsed with water 4. dried under N_2 for 10 minutes 5. vacuum RT, overnight	1. pale yellow, wets poorly 2. white 3. - 4. - 5. -	FB I
1. contacted with water 2. sonicated for 5 minutes 3. slurried for 10 minutes 4. filtered, rinsed with water 5. dried under N_2 for 10 minutes 6. vacuum RT, overnight 7. stored in freezer	1. - 2. pale yellow, turned white 3. - 4. - 5. white 6. - 7. -	FB I + other free base form
1. slurry in water, RT, 8 days; seeded with FB II 2. filtered, rinsed with water 3. vacuum RT, overnight	1. thick white slurry 2. - 3. -	FB II
2. sub sample of slurry 3. rinsed with water	2. - 3. -	FB II (indexed)

Example 14: Characterization Form I of the Free Base of Compound 1

Technique	Details	Result
XRPD	indexed	Free Base Form I

(continued)

Technique	Details	Result
XRPD	-	Free Base Form I
TGA	25 to 350 °C	0.2% weight loss up to 100 °C
DSC	25 to 350 °C	endothermic event with onset near 97 °C
Hot Stage Microscopy	22.7 °C	initial, fines, birefringent
	91.2 °C	increase in particle size and birefringence
	94.2 °C	increase in particle size and birefringence
	95.7 °C	melt onset, larger particles from initial heating
	96.1 °C	melt continuation
	96.3 °C	melt complete, no crystallization upon melting
	68.7 °C	fresh preparation, larger magnification
	91.1 °C	increase in birefringence
	94.8 °C	melt onset, larger particles, birefringent
	95.4 °C	melt continuation
	95.9 °C	only few crystals remain, cooled to 92.6 °C
	92.6 °C	held for 2 to 3 minutes crystal growth to larger blades,-began heating
	96.3 °C	complete melt
^{1}H NMR	DMSO-d6	consistent with structure
DVS	-	0.02% loss upon equilibration at 5% RH 0.22% gain from 5 to 95% RH 0.22% loss from 95 to 5%RH
	post XRPD	Free Base Form I + other Free Base Material

Example 15: Characterization of Form II of the Free Base of Compound 1

Technique	Details	Result
XRPD	indexed	Free Base Form II
XRPD	initial	Free Base Form II
	after 7 days	Free Base Form II
TGA	25 to 350 °C	0.1% weight loss up to 100 °C
DSC	25 to 350 °C	endothermic event with onset near 97 °C
^{1}H NMR	DMSO-d6	consistent with structure

Example 16: Characterization of Material N of the Free Base of Compound 1

Technique	Details	Result
XRPD	-	Free Base Material N
TGA	25 to 350 °C	0.2% weight loss up to 100 °C

(continued)

Technique	Details	Result
DSC	25 to 350 °C	endothermic event with onset near 94 °C
^{1}H NMR	DMSO-d6	consistent with structure, no residual reaction solvent observed

Example 17: Competitive Interconversion Slurries Between Free Base Forms I and II

Conditions	Solvent	Observation	XRPD Result
6 °C, 6 days	water	white	FB II
6 °C, 6 days	heptane	white	FB II
6 °C, 6 days	IPE	faint pale yellow	FB N
RT, 6 days	water	white	FB II
RT, 6 days	heptane	off white	FB II
RT, 6 days	IPE	pale yellow	FB N Error! bookmark not defined.
RT, 6 days	toluene	pale yellow	FB N
57 °C, 2 days	water	fines, off white, B	FB II + FB I
57 °C, overnight	heptane	blades and tablets, B	FB II
57 °C, overnight	IPE	blades, laminated, pale yellow, B	FB II

Example 18: Competitive Interconversion Slurries between Free Base Form II and Material N

Conditions			
35 °C, 3 days	heptane	pale yellow fines, B	FB N
57 °C, 3 days	heptane	larger blades, and rosettes of blades, B	FB II

Example 19: Selected Experimental Methods

[0099] *Indexing*: XRPD patterns are indexed by using proprietary SSCI software. Agreement between the allowed peak positions, marked with red bars within the figures, and the observed peaks indicates a consistent unit cell determination. Indexing and structure refinement are computational studies which are performed under the "Procedures for SSCI Non-cGMP Activities." To confirm the tentative indexing solution, the molecular packing motifs within the crystallographic unit cells must be determined. No attempts at molecular packing were performed.

[0100] *Differential Scanning Calorimetry (DSC):* DSC was performed using a TA Instruments Q2000 differential scanning calorimeter. Temperature calibration was performed using NIST-traceable indium metal. The sample was placed into an aluminum DSC pan, covered with a lid, and the weight was accurately recorded. A weighed aluminum pan configured as the sample pan was placed on the reference side of the cell. The data acquisition parameters and pan configuration for each thermogram are displayed in the image in the Data section of this report. The method code on the thermogram is an abbreviation for the start and end temperature as well as the heating rate; e.g., -30-250-10 means "from -30 °C to 250 °C, at 10 °C/min". The following summarizes the abbreviations used in each image for pan configurations: Tzero crimped pan (T0C); and Lid not crimped (NC).

[0101] *Dynamic Vapor Sorption (DVS):* Dynamic vapor sorption (DVS) data were collected on a VTI SGA-100 Vapor

Sorption Analyzer. NaCl and PVP were used as calibration standards. Samples were not dried prior to analysis. Adsorption and desorption data were collected over a range from 5 to 95% RH at 10% RH increments under a nitrogen purge. The equilibrium criterion used for analysis was less than 0.0100% weight change in 5 minutes with a maximum equilibration time of 3 hours. Data were not corrected for the initial moisture content of the samples.

Microscopy

[0102] *Hot Stage Microscopy:* Hot stage microscopy was performed using a Linkam hot stage (FTIR 600) mounted on a Leica DM LP microscope equipped with a SPOT Insight™ color digital camera. Temperature calibrations were performed using USP melting point standards. Samples were placed on a cover glass, and a second cover glass was placed on top of the sample. As the stage was heated, each sample was visually observed using a 20× 0.40 N.A. long working distance objective with crossed polarizers and a first order red compensator. Images were captured using SPOT software (v. 4.5.9).

[0103] *Polarized Light Microscopy:* During the course of experimentation generated samples were viewed utilizing a microscope with cross polarized light to observe morphology and birefringence. Samples were visually observed at 40x magnification. ^{1}H Solution Nuclear Magnetic Resonance (^{1}H NMR)

[0104] *SSCI:* Samples were prepared for NMR spectroscopy as ~5-50 mg solutions in the appropriate deuterated solvent. The specific acquisition parameters are listed on the plot of the first full spectrum of each sample in the data section for samples run at SSCI.

[0105] *Spectral Data Solutions:* For samples run using Spectral Data Solutions (subcontractor), the solution ^{1}H NMR spectra were acquired at ambient temperature on a Varian *UNITY*INOVA-400 spectrometer (^{1}H Larmor Frequency = 399.8 MHz). The specific acquisition parameters are listed on the spectral data sheet and on each data plot of the spectrum of the sample.

Thermogravimetric Analysis (TGA)

[0106] TG analyses were performed using a TA Instruments 2950 thermogravimetric analyzer. Temperature calibration was performed using nickel and Alumel™. Each sample was placed in an aluminum pan and inserted into the TG furnace. The furnace was heated under a nitrogen purge. The data acquisition parameters are displayed above each thermogram in the Data section of this report. The method code on the thermogram is an abbreviation for the start and end temperature as well as the heating rate; *e.g.,* 25-350-10 means "from 25 °C to 350 °C, at 10 °C/min". The use of 0 as the initial temperature indicates sample run initiated from ambient.

XRPD Analysis

[0107] *INEL:* XRPD patterns were collected with an Inel XRG-3000 diffractometer. An incident beam of Cu Kα radiation was produced using a fine-focus tube and a parabolically graded multilayer mirror. Prior to the analysis, a silicon standard (NIST SRM 640d) was analyzed to verify the Si 111 peak position. A specimen of the sample was packed into a thin-walled glass capillary, and a beam-stop was used to minimize the background from air. Diffraction patterns were collected in transmission geometry using Windif v. 6.6 software and a curved position-sensitive Equinox detector with a 2θ range of 120°. The data-acquisition parameters for each pattern are displayed above the image in the Data section of this report.

[0108] *PANalytical Transmission:* XRPD patterns were collected with a PANalytical X'Pert PRO MPD diffractometer using an incident beam of Cu radiation produced using an Optix long, fine-focus source. An elliptically graded multilayer mirror was used to focus Cu Kα X-rays through the specimen and onto the detector. Prior to the analysis, a silicon specimen (NIST SRM 640d) was analyzed to verify the Si 111 peak position. A specimen of the sample was sandwiched between 3 μm thick films and analyzed in transmission geometry. A beam-stop, short antiscatter extension, and an antiscatter knife edge were used to minimize the background generated by air. Soller slits for the incident and diffracted beams were used to minimize broadening from axial divergence. Diffraction patterns were collected using a scanning position-sensitive detector (X'Celerator) located 240 mm from the specimen and Data Collector software v. 2.2b. The data-acquisition parameters for each pattern are displayed above the image in the Data section of this report including the divergence slit (DS) before the mirror and the incident-beam antiscatter slit (SS).

[0109] *PANalytical Reflection:* XRPD patterns were collected with a PANalytical X'Pert PRO MPD diffractometer using an incident beam of Cu Kα radiation produced using a long, fine-focus source and a nickel filter. The diffractometer was configured using the symmetric Bragg-Brentano geometry. Prior to the analysis, a silicon specimen (NIST SRM 640d) was analyzed to verify the observed position of the Si 111 peak is consistent with the NIST-certified position. A specimen of the sample was prepared as a thin, circular layer centered on a silicon zero-background substrate. Antiscatter slits (SS) were used to minimize the background generated by air. Soller slits for the incident and diffracted beams were used to minimize broadening from axial divergence. Diffraction patterns were collected using a scanning position-sensitive

detector (X'Celerator) located 240 mm from the sample and Data Collector software v. 2.2b. The data acquisition parameters for each pattern are displayed above the image in the Data section of this report including the divergence slit (DS) and the incident-beam SS.

[0110] *Approximate Solubility:* A weighed sample was treated with aliquots of the test solvent at room temperature. The mixture was sonicated between additions to facilitate dissolution. Complete dissolution of the test material was determined by visual inspection. Solubility was estimated based on the total solvent used to provide complete dissolution. Some samples were then heated and observed visually for complete dissolution. The actual solubility may be greater than the value calculated because of the use of solvent aliquots that were too large or due to a slow rate of dissolution. The solubility is expressed as "less than" if dissolution did not occur during the experiment. If complete dissolution was achieved as a result of only one aliquot addition, the solubility is expressed as "greater than".

[0111] *Anti-Solvent Additions:* Compound 1/organic solvent solutions were contacted with solvents that Compound 1 was determined to be poorly soluble or insoluble in. These anti solvent additions were added to help lower the solubility of the solvent system and induce crystallization.

[0112] *Cooling and Slow Cools:* Solutions were prepared in the selected solvent or solvent/anti-solvent system. These solutions were chilled below room temperature within a refrigerator for varying lengths of time in an attempt to induce nucleation. The presence or absence of solids was noted. Upon observation of solids, in quantities sufficient for analysis, isolation of material was conduction. If insufficient quantities were present further cooling was performed in a freezer. Samples were either isolated for analysis wet or as dry powders.

[0113] *Compression:* Selected samples were compressed utilizing a KBr die and a Carver hydraulic press. An applied load of 10000 lbs was applied to the die shaft for approximately 20 minutes.

[0114] *Crystallization from Solution:* Saturated solutions were generated at ambient and then capped. Nucleation was observed to occur from these systems during evaluation of the Free Base of Compound 1.

[0115] *Fast Evaporation:* Solutions were prepared in selected solvents and agitated between aliquot additions to assist in dissolution. Once a mixture reached complete dissolution, as judged by visual observation, the solution was allowed to evaporate at ambient temperature in an uncapped vial or at ambient under nitrogen. The solids that formed were isolated for evaluation.

[0116] *Milling:* Selected material was milled utilizing a Reitch Mill. The material was loaded into an agate lined milling vessel followed by the addition of an agate ball. The vessel was then placed on to the mill and milled for approximately 30 minutes at frequency of 1/30 seconds. The milling was stopped approximately every 10 minutes and material scraped from the wall before further milling.

[0117] *Slurry:* Solutions were prepared by adding enough solids to a given solvent so that excess solids were present. The mixture was then agitated in a sealed vial at either ambient or an elevated temperature. After a given amount of time, the solids were isolated for analysis.

[0118] *Temperature and Relative Humidity Stress:* Selected materials were stressed at elevated related humidity and/or temperature. Relative humidity jars (saturated salt solutions used to generate desired relative humidity) were utilized to store selected samples. The following relative humidity jars were utilized during evaluation: 75% RH (NaCl) and 60% (NaBr), to investigate the effects of humidity. Temperatures utilized were ambient, 30, 40, 60, and 100-125 °C.

[0119] *Vacuum:* Selected materials were stressed under reduced pressure for a set time period. Initial stressing was conducted with the in-house vacuum system with absolute pressure readings <67 Pa (500 mTorr), typically 4 to 6.7 Pa (30 to 50 mTorr (0.030 to 0.05 mmHg)). Additional vacuum stressing was conducted at 48 mmHg utilizing a portable lab vacuum and bleed to simulate conditions similar to those expected during process.

Example 20: **Disproportionation** of the **HCl** salt

[0120] The disproportionation of the HCl salt in water was utilized to generate free base. The nucleation of Free Base Form I occurs first. Extending the slurry time induces the transformation to a more thermodynamically stable phase relative to Form I, Free Base Form II.

[0121] Three anhydrous materials of the free base were identified; Free Base Forms I, II, and Material N. Free Base Material N appears to be most stable form, relative to Forms I and II, at room temperature. Free Base Material N is enantiotropic relative to Form II, and will transform reversibly at a specific transition temperature (estimated near 42 °C). Above the transition temperature, Free Base Form II appears to be the most stable form, relative to Form I and Material N.

[0122] The HCl salt (termed "HCl Form I") was subjected to various stress conditions and monitored by XRPD to evaluate physical stability. As discussed, disproportionation occurred during the DVS experiment of the HCl salt, indicating instability upon exposure to elevated humidity. Disproportionation is further evident with wet milling or in direct contact with water (e.g. slurry) as shown by the presence of Free Base Forms I or II, identified by XRPD. The volatilization and loss of HCl upon heating and/or vacuum is shown by the presence of Free Base Form I, identified by XRPD, and also indicates instability at these conditions.

- Contact with water resulted in a visual color change of the material from pale yellow to white; physical changes were also observed microscopically. Immediate disproportionation occurs. XRPD analysis identified the resulting material from a water slurry (~5 minutes) as Free Base Form I. Free Base Form II also becomes evident if the amount of time in the slurry is extended.

- The volatilization of HCl was evident within hours of exposure to drying conditions. Conversion to Free Base Form I was observed by XRPD at 30 °C (after 12 hrs), 40 °C (after 6 hrs), and at 40 °C/48 mmHg (after 6 hrs).

- Free Base Material C becomes evident at more extreme conditions involving elevated temperatures. Heating HCl Form I up to 125 °C induces the loss of acidic volatiles (judged visually by use of pH paper held above sample). XRPD analysis identifies the resulting sample as a mixture of HCl Form I, Free Base Form I, and Free Base Material C. Exposing the HCl salt to 60 °C under vacuum for 6 days provides the same result. The nature of Material C is not established

[0123] The HCl salt was shown to disproportionate immediately in water. This phenomenon was utilized to generate free base. The nucleation of Free Base Form I occurs first. Extending the slurry time induces the transformation to a more thermodynamically stable phase relative to Form I, Free Base Form II.

- A 20 ml vial was charged with 266.4 mg of HCl Form I and contacted with 10 ml of water. The sample was sonicated until the pale yellow material changed color to white. The resulting solids were collected by filtration (water aspirated) and rinsed with 10 ml of water. A nitrogen purge was blown over the sample for approximately 10 minutes prior to exposure to vacuum at ambient temperature to dry overnight. The resulting material was analyzed by XRPD and determined to be Free Base Form I.

- A 250 ml Erlenmeyer flask was charged with 6.0250 grams of HCl Form I and contacted with 220 mL of water. The sample was sonicated for approximately 5 minutes to disperse the material. The yellow material changed color to white during sonication. A stir bar was added and the sample was stirred at 700 RPM for approximately 10 minutes. The solids were collected by filtration and rinsed with 220 ml of water followed by a nitrogen purge over the sample for approximately 10 minutes prior to exposure to vacuum at ambient temperature. The sample was dried at this condition for approximately 24 hours yielding 5.1834 grams of material. The resulting material was analyzed by XRPD and determined to be a mixture of Free Base Form I and Free Base Material D. (The nature of Material D is not established.)

[0124] The procedure used to generate Free Base Form II is described below.

- A 20 ml vial was charged with 477.5 mg of HCl Form I lot 20 and contacted with 20 ml of water. The sample was sonicated until the pale yellow material changed color to white. A small amount of sample (mixture of Free Base Forms I and II) was added as seeds. A stir bar was added and the sample was stirred at 200 RPM for 8 days. The resulting solids were collected by filtration (water aspirated) and rinsed with 15 ml of water. The sample was exposed to vacuum at ambient temperature to dry overnight. The resulting material was analyzed by XRPD and determined to be Free Base Form II.

Example 21: Additional Procedures for the Preparation of the free base of Form I, Form II, and From N

Conversion of the free base of Compound 1 to the HCl salt

[0125] *General Procedure:* Slowly treat a solution of the free base of Compound 1 in MEK (5 vol) with conc HCl (1.5 eq). Cool the resulting slurry to 0-5 °C for 1 h and filter. Wash solids with MEK (1 vol). Dry under vacuum at 30-35 °C.
[0126] *Preparation A:* Following the general procedure above, 35 g of crude Compound 1 was processed to provide the HCl salt as a pale yellow solid (32.4 g, 82% yield, 99.8% purity by HPLC).

Preparation of the free base Form I from the HCl Salt of Compound 1

[0127] *General Procedure:* Vigorously stir a slurry of the HCl salt of Compound 1 in DIW (10 vol) for 5 min to 2 h. Filter the slurry, wash with DIW (2×1 vol), dry on funnel, then further dry under vacuum at 30-35 °C.
[0128] *Preparation A:* Following the general procedure above, after stirring for 1h, 32 g of the HCl salt of Compound 1 was processed to provide the free base as a pale yellow solid (27.3 g, 95% yield, 99.8% purity by HPLC; DSC indicates Form I).

[0129] *Preparation B:* Following the general procedure above, after stirring for 1h, 39 g of the HCl salt of Compound 1 was processed to provide the free base as a pale yellow solid (31.8 g, 90% yield, >99.9% purity by HPLC)).

[0130] *Preparation C:* Thus, the HCl salt of Compound 1 (134 g) was vigorously stirred in water (10 vol) until the material appeared as a finely dispersed white slurry. After filtration and drying, a white crystalline solid (116 g, 96% recovery, >99.9% purity by HPLC) was isolated.

[0131] *Preparation D:* The purpose of this experiment was to prepare the free base from Compound 1, HCl. Thus, the HCl salt of Compound 1 (65.3 g) was vigorously stirred in water (10 vol) until the material appeared as a finely dispersed white slurry. After filtration and drying, a white crystalline solid (57.5 g, 97.6% recovery, >99.9% purity by HPLC) was isolated.

Preparation of GBT000440 free base Form II from GBT000440 free base Form I

[0132] *General Procedure:* Stir a slurry of the free base of Compound 1 Form I in an appreciate solvent (e.g. heptane or water) (10 vol) for 1-7 days. Filter the slurry, wash with DIW (2×1 vol), dry on funnel, then further dry under vacuum at 30-35 °C.

[0133] *Preparation A:* Thus, the free base of Compound 1, Form I (114 g) was stirred in n-heptane (10 vol) at 35 °C. After 4 days, XRPD indicated the material was Form II. The slurry was filtered and dried to provide 110 g off white solid.

[0134] *Preparation B:* the free base of Compound 1 (5 g) was slurried in heptanes (10 vol 50mlL) at room temperature. After 4 days, the slurry was filtered to provide an off-white solid.

[0135] *Preparation C:* the free base of Compound 1 (5.8 kg) was slurried in heptanes (10 vol) at room temperature. After 2 days, the slurry was filtered and washed with 2x2 vol n-heptane to provide 4.745 kg of Form II as an off-white solid.

[0136] *Preparation D:* the free base of Compound 1 (5 g) was slurried in water. After 4 days, the slurry was filtered to provide an off-white solid. *Preparation of GBT000440 free*

base Form N from GBT000440 free base Form I or Form II

[0137] *General Procedure:* Stir a slurry of the free base of Compound 1, Form I in MTBE (4 vol) at room temperature for at least 4 days. After 4 days, filter the slurry to provide an off-white solid. Obtain XRPD to confirm polymorph as Material N.

[0138] *Preparation A:* Following the general procedure above, 27 g of the free base of Compound 1, Form I (48TRS079) was stirred in MTBE at 18-23 °C for 4 days. DSC indicated it should be Material N. Isolated 22.2 g cream colored solid (82% recovery, 99.9 purity by HPLC). XRPD analysis planned.

[0139] *Preparation B:* Following the general procedure above, 31 g of the free base of Compound 1, Form I was stirred in 3 vol MTBE at 18-23 °C for 4 days.

[0140] *Preparation C:* the free base of Compound 1, Form I (13KWB023, 1 g) was slurried in MTBE (5 vol) at room temperature. Slurry was seeded with Material N (50 mg). After 4 days, the slurry was filtered to provide a off-white solid. DSC indicated the melting point was the same as Material N.

[0141] *Preparation D:* The purpose of this experiment was to convert the the free base of Compound 1, Form II to Material N. Thus, the free base of Compound 1 (0.5 g) was stirred in 5 vol of di-*n*-propyl ether at 18-23 °C. After 2 days, DSC corresponded to the pattern observed for Material N. XRPD analysis confirmed Material N had been formed.

[0142] *Preparation E:* To the free base of Compound 1, Form II (5 g) was added diisopropyl ether (5 vol, 25 mL) at room temperature. After 4 days, the slurry was filtered to provide a off-white solid. DSC indicates Material N.

Example 22: Preliminary Solvent-based Screens

[0143] Rapid, solvent-based screens were conducted in an attempt to determine the most stable form of the free base of Compound 1. The study also provides a preliminary assessment of the propensity of these materials to exist in various crystal forms. Generated solids were observed by polarized light microscopy (PLM) and/or analyzed by X-ray powder diffraction (XRPD), comparing the resulting XRPD patterns to known patterns of Compound 1.

[0144] If possible, XRPD patterns were indexed. Indexing is the process of determining the size and shape of the crystallographic unit cell given the peak positions in a diffraction pattern. The term gets its name from the assignment of Miller index labels to individual peaks. XRPD indexing serves several purposes. If all of the peaks in a pattern are indexed by a single unit cell, this is strong evidence that the sample contains a single crystalline phase. Given the indexing solution, the unit cell volume may be calculated directly and can be useful to determine their solvation states. Indexing is also a robust description of a crystalline form and provides a concise summary of all available peak positions for that phase at a particular thermodynamic state point.

[0145] Materials exhibiting unique crystalline XRPD patterns, based on visual inspection of peaks associated with these materials, were given letter designations. The letter designation is tentatively associated with the word 'Material'

if insufficient characterization data is available. The nomenclature is used only to aid in the identification of unique XRPD patterns and does not imply that the stoichiometry, crystalline phase purity, or chemical purity of the material is known. Materials are further designated as forms with Roman numeral designations (i.e., Free Base Material A = Free Base Form I), when phase purity (obtained through indexing of the XRPD pattern or single crystal structure elucidation) and chemical identity/purity (obtained through proton NMR spectroscopy) of the material is determined.

[0146] Three anhydrous materials were identified: Forms I, II, and Material N. Material N appears to be most stable form, relative to Forms I and II, at room temperature. Material N is enantiotropic relative to Form II, and will transform reversibly at a specific transition temperature (estimated near 42 °C). Above the transition temperature, Form II appears to be the most stable form, relative to Form I and Material N.

[0147] Materials C and D are used to identify a few additional, low intensity peaks observed in XRPD patterns which were predominantly composed of the Free Base Form I of Compound 1 or mixtures of the HCl Form I and Free Base Form I of Compound 1.

Example 23: Anhydrous Ansolvate Forms

Form I

[0148] Free Base Form I is a metastable, anhydrous phase of the free base that is formed immediately from the disproportionation of the HCl salt in water. A representative XRPD pattern of Form I was successfully indexed and the unit cell volume is consistent with anhydrous free base. Visual comparison of the XRPD pattern to the historical pattern of the free base provided indicates the material may be similar; however, the historical pattern appears to exhibit additional peaks from a potential mixture.

[0149] The ^{1}H NMR spectrum is consistent with the chemical structure of Compound 1.

[0150] The chemical shift at approximately 2.5 ppm is assigned to DMSO (due to residual protons in the NMR solvent). Peaks that could be associated with residual solvents were not visible, consistent with the anhydrous unit cell volume determined from the indexing solution above and the negligible wt% loss observed by TGA discussed below.

[0151] Thermograms (TG) data shows negligible weight loss, 0.2%, up to 100 °C, consistent with an anhydrous form. The DSC exhibits a single endotherm with an onset near 97 °C (similar to what is observed for Form II). The endotherm is consistent with a melt by hot stage microscopy. However, changes in particle size and birefringence were evident prior to the melt; a possible phase change occurred. Consequently, if a phase change occurred and an endotherm similar to that of Free Base Form II was observed, it can be inferred that the observed melt is truly not of Form I but of the resulting phase, most likely Form II.

[0152] The DVS isotherm indicates Form I is not hygroscopic. Negligible weight gain and loss, 0.2%, was observed through sorption/desorption. By XRPD, the material recovered from the DVS experiment was predominately Free Base Form I with a few additional peaks. The additional peaks were termed Free Base Material D. The nature of Material D is unknown; however, the appearance of another phase(s) indicates that Form I is not likely physically stable at elevated humidity conditions (at ambient temperature).

Form II

[0153] Free Base Form II is an anhydrous phase of the free base. Form II is enantiotropically related to Material N, where it is the thermodynamically stable form above an estimated transition temperature of 42 °C. Form II can be generated in solvents that do not form known solvates; such as heptane, IPE, MTBE, or toluene; through short-term slurry conversions of Form I (where the crystallization kinetics delay the nucleation of the more stable form) or elevated temperature slurries (above 42 °C). A representative XRPD pattern of Form II was successfully indexed and the unit cell volume is consistent with anhydrous free base of Compound 1.

[0154] The ^{1}H NMR spectrum is consistent with the chemical structure of Compound 1. The chemical shift at approximately 2.5 ppm is assigned to DMSO (due to residual protons in the NMR solvent). Peaks that could be associated with residual solvents were not visible, consistent with the anhydrous unit cell volume determined from the indexing solution above and the negligible wt% loss observed by TGA discussed below.

[0155] Thermograms (TG) data show negligible weight loss, 0.1%, up to 100 °C, consistent with an anhydrous form. The DSC exhibits a single endotherm (80.1 J/g) with an onset near 97 °C.

[0156] Form II remained unchanged after 7 days at ambient storage, through reanalysis by XRPD. The form is known to be thermodynamically metastable, relative to Material N, at this condition; however, the kinetics of polymorph conversion may be slow at ambient conditions in the solid state.

Material N

[0157] Free Base Material N is an anhydrous phase of the free base. Material N is enantiotropically related to Form II, where it is the thermodynamically stable form below an estimated transition temperature of 42 °C. Given the opportunity, Material N can be generated through slurries in solvents that do not form known solvates; such as heptane, IPE, MTBE, or toluene; at temperatures below 42 °C. The following is an example of a laboratory scale procedure used to generate Free Base Material N.

- 53.0 mg of Free Base Form I was contacted with 2 ml of an IPE/free base solution (concentration 13 mg/ml). A stir bar was added and the sample was slurried for 7 days at ambient. The solution was decanted from the sample and the remaining solids briefly dried under nitrogen. Characterization Data indicates Material N is a unique crystalline phase.

[0158] The ^{1}H NMR spectrum is consistent with the chemical structure of Compound 1. The chemical shift at approximately 2.5 ppm is assigned to DMSO (due to residual protons in the NMR solvent). Peaks that could be associated with residual solvents were not visible, consistent with the negligible wt% loss observed by TGA discussed below.
[0159] Thermograms (TG) data show negligible weight loss, 0.2%, up to 100 °C, consistent with an anhydrous form. The DSC exhibits a single endotherm (82.8 J/g) with an onset at 94 °C.
[0160] Tentative Determination of the Thermodynamic Relationship between Free Base Forms I, II, and Material N
[0161] Characterization data indicates that Forms I, II, and Material N are unique crystalline phases; however, only the XRPD patterns of Forms I and II were successfully indexed to confirm phase purity. Therefore, any proposed thermodynamic relationship between these materials is a working hypothesis, where the phase purity of Material N is assumed.
[0162] Phase transitions of solids can be thermodynamically reversible or irreversible. Crystalline forms which transform reversibly at a specific transition temperature (T_p) are called enantiotropic polymorphs. If the crystalline forms are not interconvertable under these conditions, the system is monotropic (one thermodynamically stable form). Several rules have been developed to predict the relative thermodynamic stability of polymorphs and whether the relationship between the polymorphs is enantiotropic or monotropic. The heat of fusion rule is applied within this study. The heat of fusion rule states that if the higher melting form has the lower heat of fusion then the two forms are enantiotropic, otherwise they are monotropic.
[0163] Material N appears to be most stable form, relative to Forms I and II, at room temperature. Based on the heats of fusion and melts determined by DSC, Material N is enantiotropic relative to Form II, and will transform reversibly at a specific transition temperature ($T^{N\text{-}II}$). Due to a possible phase change of Form I to Form II that occurred prior to the observed endotherm in the DSC, the relationship of Form I with either Material N or Form II cannot be conclusively determined through the heat of fusion rule. However, through various interconversion slurries, it was shown that Form I is the least thermodynamically stable form between 6 °C and $T^{N\text{-}II}$. In addition, assuming that Form I spontaneously converted to Form II in the DSC at elevated temperatures (prior to the observed melt), it must follow that Form II is also more stable than Form I above $T^{N\text{-}II}$.

Example 24: Estimated Transition Temperature

[0164] The estimated transition temperature between two enantiotropically related forms can be calculated from their melt onsets and heats of fusion based on the equation shown below.

$$T_p = \frac{\Delta H_{f,2} - \Delta H_{f,1} + (C_{p,liq} - C_{p,1}) \cdot (T_{f,1} - T_{f,2})}{\frac{\Delta H_{f,2}}{T_{f,2}} - \frac{\Delta H_{f,1}}{T_{f,1}} + (C_{p,liq} - C_{p,1}) \cdot \ln\left(\frac{T_{f,1}}{T_{f,2}}\right)}$$

Where,

$$\left(C_{p,liq} - C_{p,1}\right) = k \cdot \Delta H_{f,1} \quad \text{and } k = 0.005$$

[0165] Between Material N and Form II, the equation estimates a transition temperature of 42 °C. To summarize, the

relative stability of the forms from most to least stable is shown below.

Temperature Range*	Relative Stability	Comments
Below 6 °C	N > II	Relationships to Form I are not established below this temp
Between 6 °C and $T^{N\text{-}II}$	N > II > I	-
Above $T^{N\text{-}II}$	(II > N) *and* (II > I)	Relationship between Form I and Material N is not established above this temp
* $T^{N\text{-}II}$ is estimated to be near 42 °C		

Example 25: Energy - Temperature Diagram

[0166] The Energy - Temperature Diagram of FIG. 17 is a semi-quantitative graphical solution of the Gibbs - Helmholtz equation, where the enthalpy (*H*) and free energy (*G*) isobars for each form are depicted as a function of temperature.

Example 26: Competitive Interconversion Slurry Experiments

[0167] Interconversion experiments were performed to support the thermodynamic relationship between polymorphs illustrated by the Energy - Temperature Diagram above. Interconversion or competitive slurry experiments are a solution-mediated process that provides a pathway for the less soluble (more stable) crystal to grow at the expense of the more soluble crystal form. Outside the formation of a solvate or degradation, the resulting more stable polymorph from an interconversion experiment is contemplated to be independent of the solvent used because the more thermodynamically stable polymorph has a lower energy and therefore lower solubility. The choice of solvent affects the kinetics of polymorph conversion and not the thermodynamic relationship between polymorphic forms.

[0168] The results of the interconversion studies are consistent with the tentative Energy - Temperature Diagram shown herein. Binary slurries were prepared at ambient, 6, and 57 °C using Forms I and II. Form II resulted from the majority of these experiments, confirming that Form II is more stable relative to Form I within this temperature range.

[0169] A few of the experiments conducted at ambient and 6 °C resulted in Material N. Although this does not provide specific clarification between Forms I and II, it does provide evidence that Material N is the most stable form relative to both Forms I and II at these temperatures (which were conducted below the estimated transition temperature of 42 °C). Additional interconversion slurries between Form II and Material N were conducted at temperatures which bracket this estimated transition temperature and confirm that Form II and Material N are enantiotropically related.

Example 27: Solid-state Nuclear Magnetic Resonance

[0170] ^{13}C and ^{15}N spectra acquired for the three polymorphic forms I, II and Material N. See FIGS. 10 and 11. Spectra were acquired at 253K to prevent any low temperature transitions occurring during measurement and acquisition parameters optimised for each polymorphic form.

[0171] Based on solid-state nuclear magnetic resonance, all three forms are crystalline and are distinct polymorphic forms. Form I contains one molecule per asymmetric unit, Form II contains two molecules per asymmetric unit and Form N contains four molecules per asymmetric unit. See the ^{15}N spectra in FIG. 11.

Example 28: Chemical and Physical Stability Evaluation of the Free Base Form I of Compound 1

[0172] A mixture predominately composed of Free Base Form I (with Free Base Material D) were exposed to stability conditions to assess physical and chemical stability. Three conditions were used; open to 25 °C / 60% RH, open to 40 °C / 75% RH, and closed to 60 °C. Physical stability was evaluated by XRPD. Chemical stability was determined through UPLC and ^{1}H NMR, when applicable. Materials were tested after 1, 7, and 14 days of exposure.

Chemical Stability of Free Base Form I

[0173] For the free base stability sample, UPLC showed very low levels of impurities present. The level of impurities did not rise significantly after 14 days of age. This would seem to indicate good chemical stability against the conditions used for stability assessment. The ^{1}H NMR spectra of samples exposed to 60 °C (14 days) were also consistent with this conclusion.

Physical Stability of Free Base Form I

[0174] The free base of Compound 1 remained unchanged, by XRPD, at 25 °C / 60% RH. However, differences were observed at the other two conditions. The few, minor peaks attributed to Free Base Material D were no longer observed, indicating that Material D is metastable and is not sustained at elevated temperatures. In addition, Free Base Form II was observed after 7 days of age. This is consistent with the conclusions discussed herein, where Free Base Form II is more stable relative to Free Base Form I at these temperatures.

Example 29: Physical Stability Evaluation of the Free Base Form II and Material N (Form N) of Compound 1

[0175] DSC was modulated at low underlying heating rate, followed by X-ray powder diffraction. A low underlying heating rate was used of of 0.02 °C min^{-1}. The temperature was 80 °C for form N and 90 °C for form II. Exposure was essentially isothermal, covering a temperature range with sensitivity to detect changes in physical form. The resultant materials were examined by X-ray powder diffraction. No changes in physical form were observed for either polymorphic form II or polymorphic form N (*i.e.,* material N).

[0176] Forms II and N were exposed to 40 °C/75% relative humidity (RH), 80 °C, 80 °C /80%RH for 9 days followed by X-ray powder diffraction. No changes in physical form were observed for either polymorphic form II or polymorphic form N.

[0177] The thermodynamic barrier for inter-conversion between polymorphic form II and form N is high, and physical stability is good for both forms. Thermally induced inter-conversion between form II and form N is unlikely to occur.

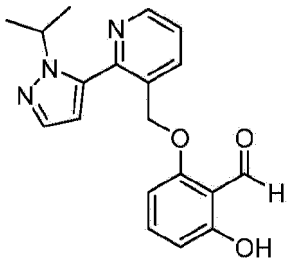
Example 30: The Relative Thermodynamic Stability of Polymorphic Forms II and N.

[0178] Extended solvent mediated maturation studies were conducted with 1:1 w/w mixtures of polymorphic form II and form N. Hexane provided a good medium for solvent assessments. The temperatures used include -20 °C, -10 °C, 0 °C, 10 °C, 20 °C, 30 °C, 40 °C and 50 °C. Significantly increased solubility was observed at 30 °C, 40 °C and 50 °C. Solids derived from maturation at -20 °C, -10 °C, 0 °C, 10 °C, 20 °C were analyzed by X-ray powder diffraction. In each case, significant conversion to Form N was observed.

[0179] Form N is thermodynamically more stable than form II at temperatures of 20 °C and lower. An enantiotropic relationship between the two forms is likely to exhibit equivalence in thermodynamic stability at ca. 30-40 °C .

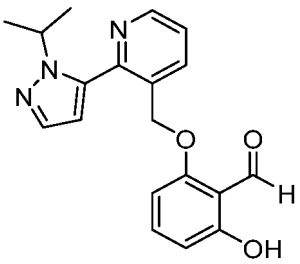
Example 31: Morphology of Form N

[0180] Initial examination of a batch of polymorphic form N indicates an acicular morphology.



Claims

1. Crystalline Form II of the free base of Compound 1:



Compound 1

wherein Form II is **characterized by** X-ray powder diffraction peaks Cu Kα radiation at 13.37°, 14.37°, 19.95° and 23.92°2θ, each ±0.2 °2θ.

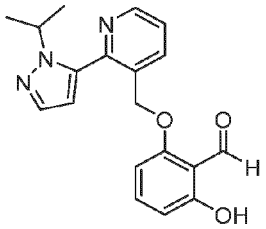
2. The crystalline Form II of claim 1, **characterized by** an endothermic peak at 97 ±2 °C as measured by differential scanning calorimetry using a TA Instruments Q2000 differential scanning calorimeter at a heating rate of 10 °C/min with temperature calibration performed using NIST-traceable indium metal.

3. A composition comprising the crystalline Form II of any one of the preceding claims.

4. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and the crystalline Form II of any one of claims 1-2.

Patentansprüche

1. Kristalline Form II der freien Base von Verbindung 1:



Verbindung 1

wobei Form II durch Röntgenpulverbeugungspeaks Cu-Kα-Strahlung bei 13,37°, 14,37°, 19,95° und 23,92° 2θ, jeweils ± 0,2° 2θ, gekennzeichnet ist.

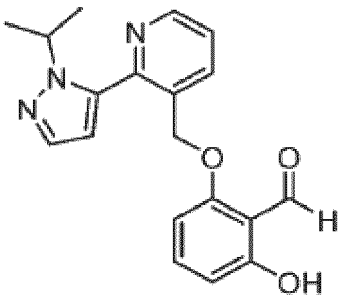
2. Kristalline Form II nach Anspruch 1, **gekennzeichnet durch** einen endothermen Peak bei 97 ± 2 °C gemäß Messung durch Differentialkalorimetrie unter Verwendung eines Differentialkalorimeters der Bauart TA Instruments Q2000 bei einer Aufheizrate von 10 °C/min, wobei die Temperaturkalibrierung unter Verwendung von NIST-rückverfolgbarem Indiummetall durchgeführt wird.

3. Zusammensetzung, umfassend die kristalline Form II nach einem der vorhergehenden Ansprüche.

4. Pharmazeutische Zusammensetzung, umfassend einen pharmazeutisch unbedenklichen Hilfsstoff und die kristalline Form II nach einem der Ansprüche 1-2.

Revendications

1. Forme cristalline II de la base libre du Composé 1 :



Composé 1

la Forme II étant **caractérisée par** des pics de diffraction des rayons X sur poudre de rayonnement Cu Kα à 13,37°, 14,37°, 19,95° et 23,92° 2θ, chacun $\pm$ 0,2 °2θ.

2. Forme cristalline II selon la revendication 1, **caractérisée par** un pic endotherme à 97 $\pm$ 2 °C tel que mesuré par calorimétrie différentielle à balayage à l'aide d'un calorimètre différentiel à balayage TA Instruments Q2000 à une vitesse de chauffage de 10 °C/min avec un étalonnage de température réalisé à l'aide de métal de type indium traçable au NIST.

3. Composition comprenant la Forme cristalline II selon l'une quelconque des revendications précédentes.

4. Composition pharmaceutique comprenant un excipient pharmaceutiquement acceptable et la Forme cristalline II selon l'une quelconque des revendications 1 et 2.

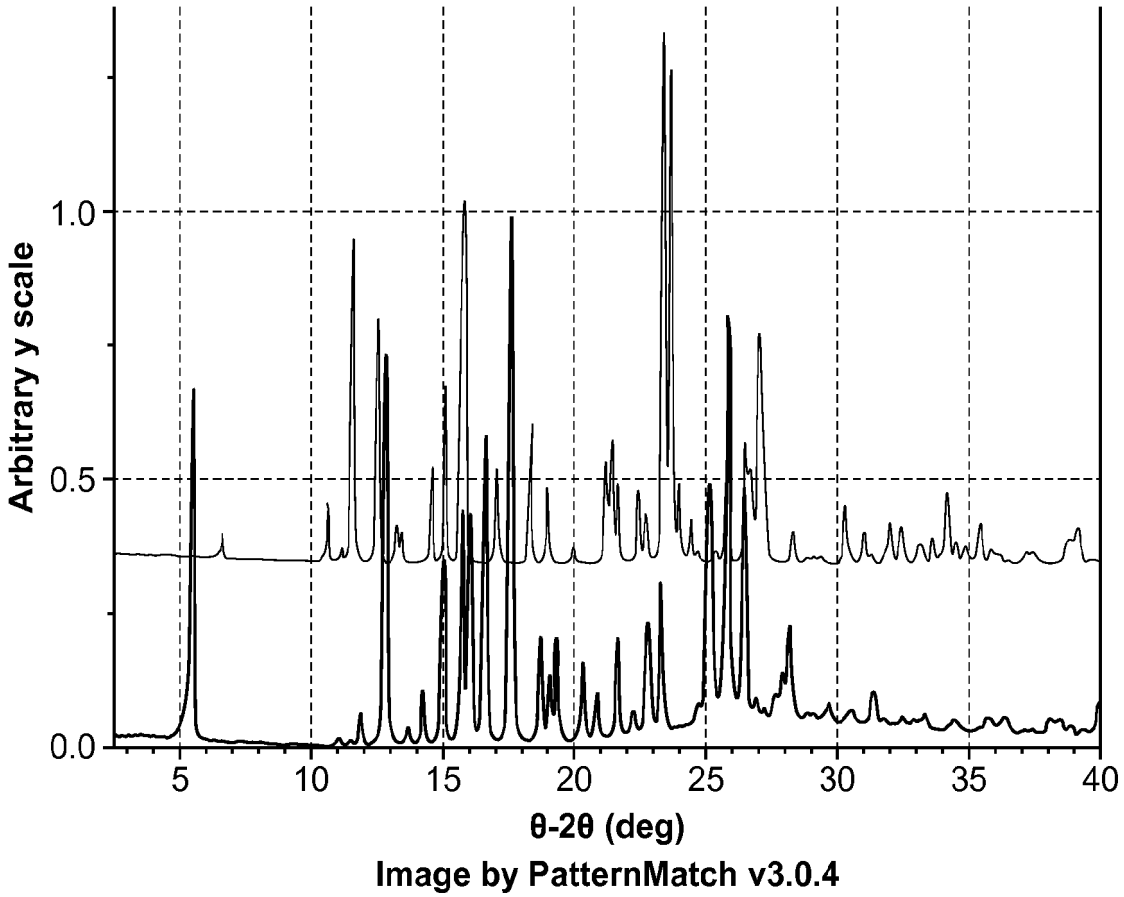

Arbitrary y scale
1.0
0.5
0.0
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 1

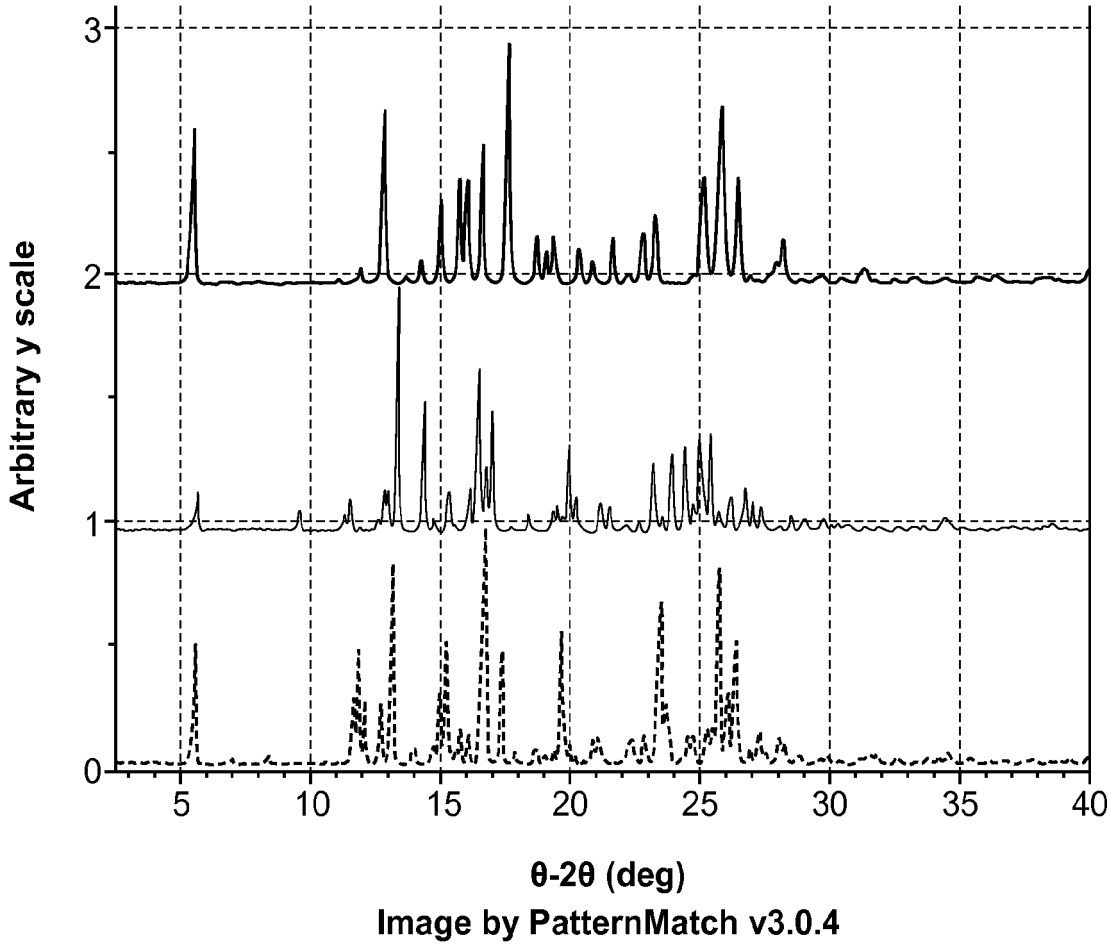
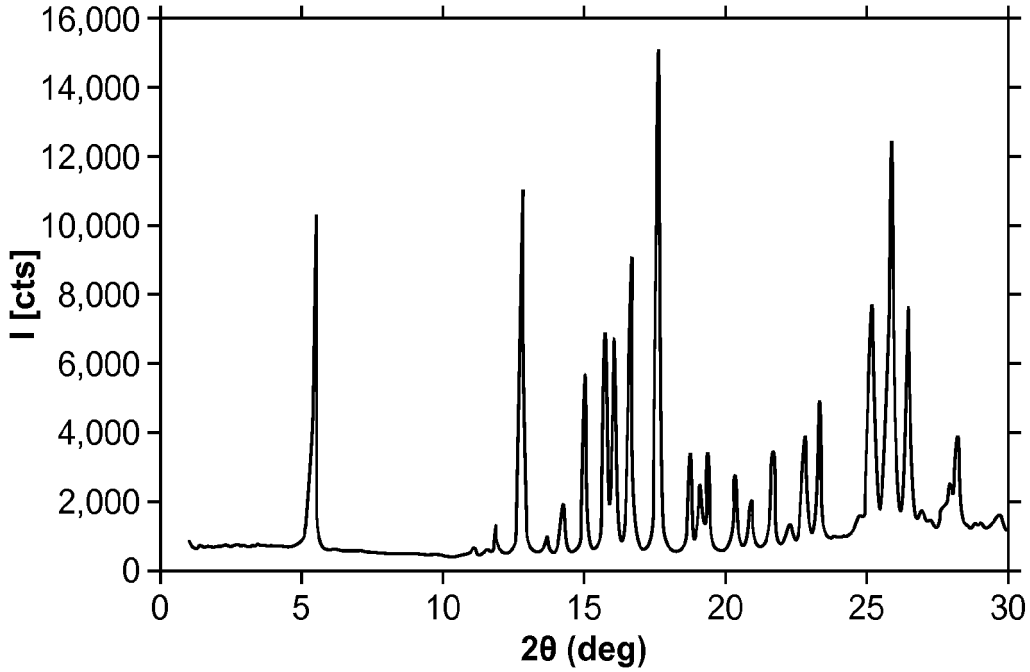
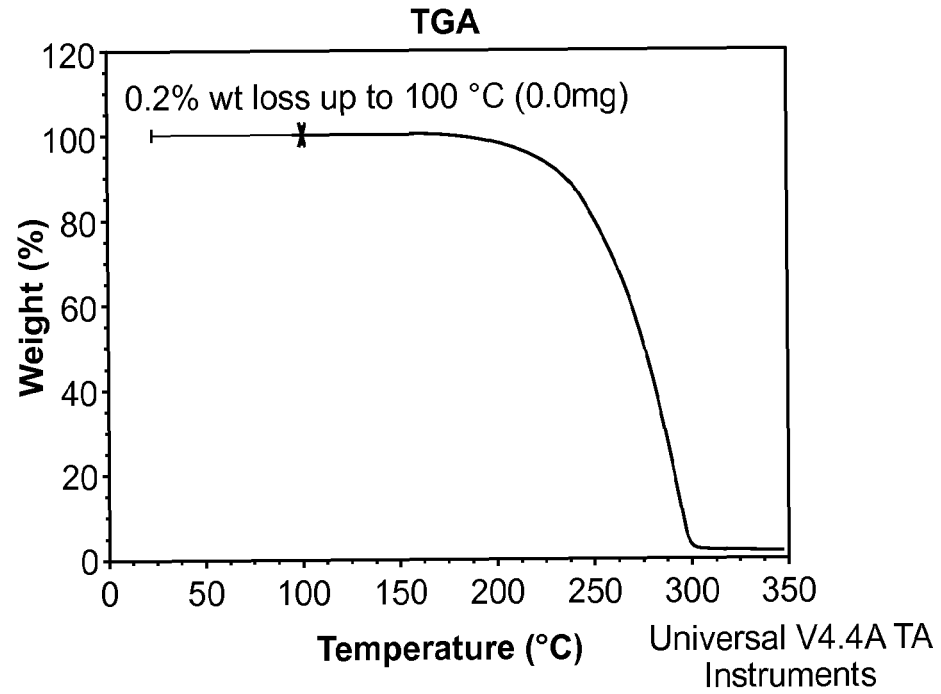

Arbitrary y scale
3
2
1
0
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 2



Bravais Type	Primitive Monoclinic
a [Å]	7.760
b [Å]	31.978
c [Å]	7.177
α [deg]	90
β [deg]	100.16
γ [deg]	90
Volume [$Å^3$/cell]	1,753.0
Chiral Contents?	Achiral
Extinction Symbol	P 1 2_1/c 1
Space Group(s)	$P2_1$/c (14)
Source	Manual Input

FIG. 3


TGA
0.2% wt loss up to 100 °C (0.0mg)
Weight (%)
120
100
80
60
40
20
0
0
50
100
150
200
250
300
350
Temperature (°C)
Universal V4.4A TA Instruments

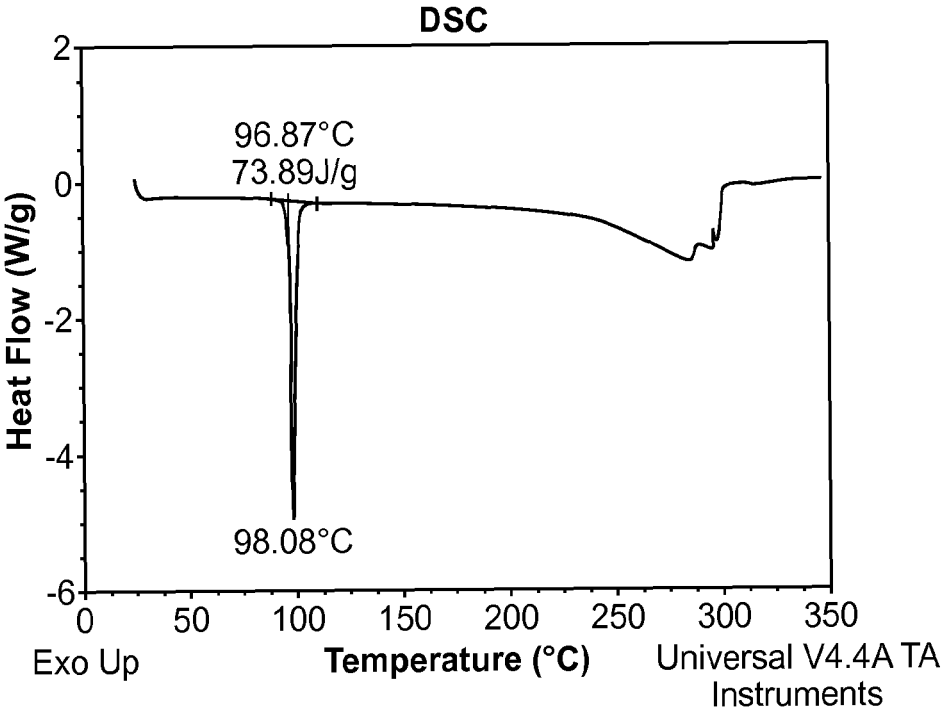
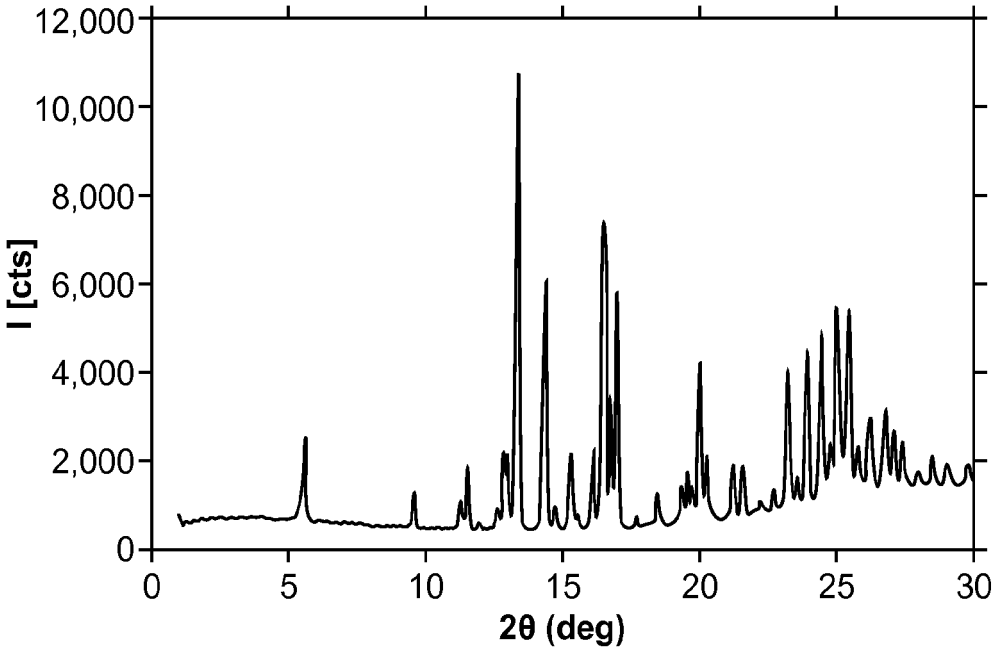
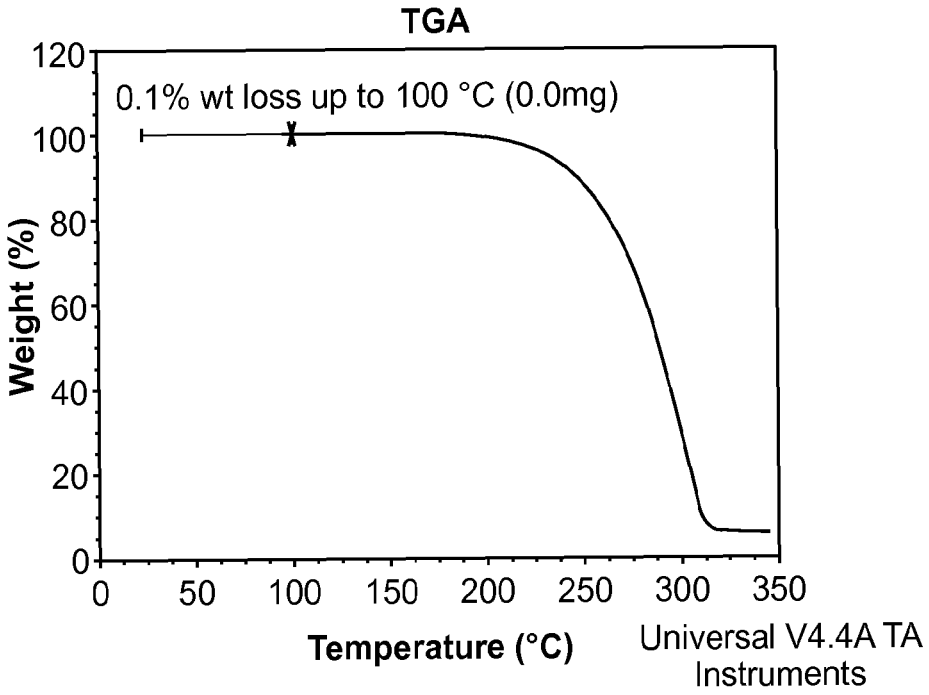

DSC
96.87°C
73.89J/g
98.08°C
Heat Flow (W/g)
2
0
-2
-4
-6
0
50
100
150
200
250
300
350
Exo Up
Temperature (°C)
Universal V4.4A TA Instruments

FIG. 4



Bravais Type	Triclinic
a [Å]	7.876
b [Å]	14.555
c [Å]	16.281
α [deg]	104.23
β [deg]	92.96
γ [deg]	101.38
Volume [$Å^3$/cell]	1,763.8
Chiral Contents?	Not Specified
Extinction Symbol	P -
Space Group(s)	P1 (1)P$\bar{1}$(14)
Source	Triads Algorithm

FIG. 5


TGA
0.1% wt loss up to 100 °C (0.0mg)
Weight (%)
120
100
80
60
40
20
0
0
50
100
150
200
250
300
350
Temperature (°C)
Universal V4.4A TA Instruments

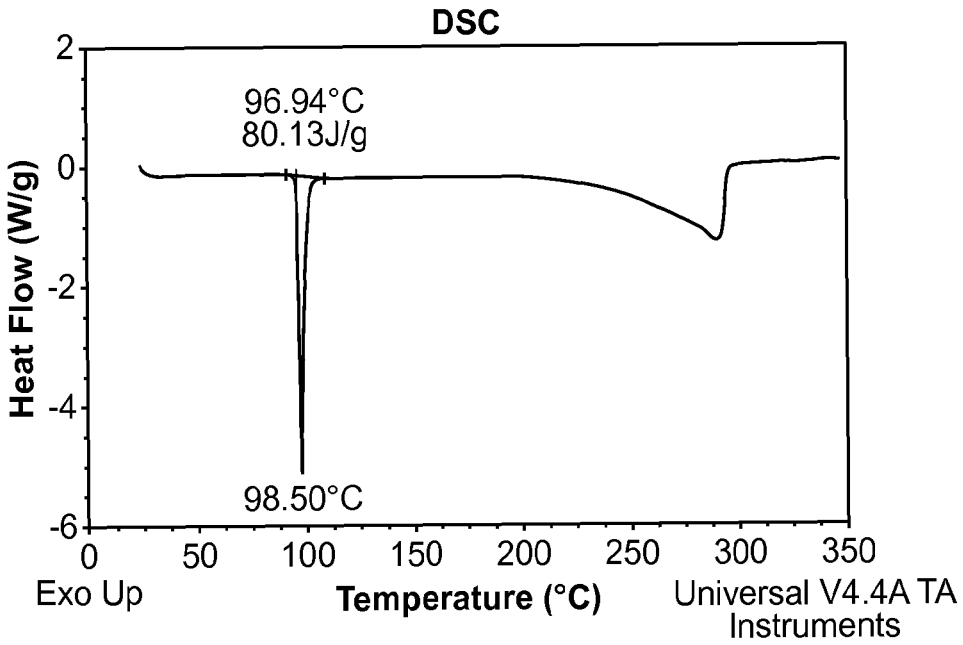

DSC
96.94°C
80.13J/g
98.50°C
Heat Flow (W/g)
2
0
-2
-4
-6
0
50
100
150
200
250
300
350
Exo Up
Temperature (°C)
Universal V4.4A TA Instruments

FIG. 6

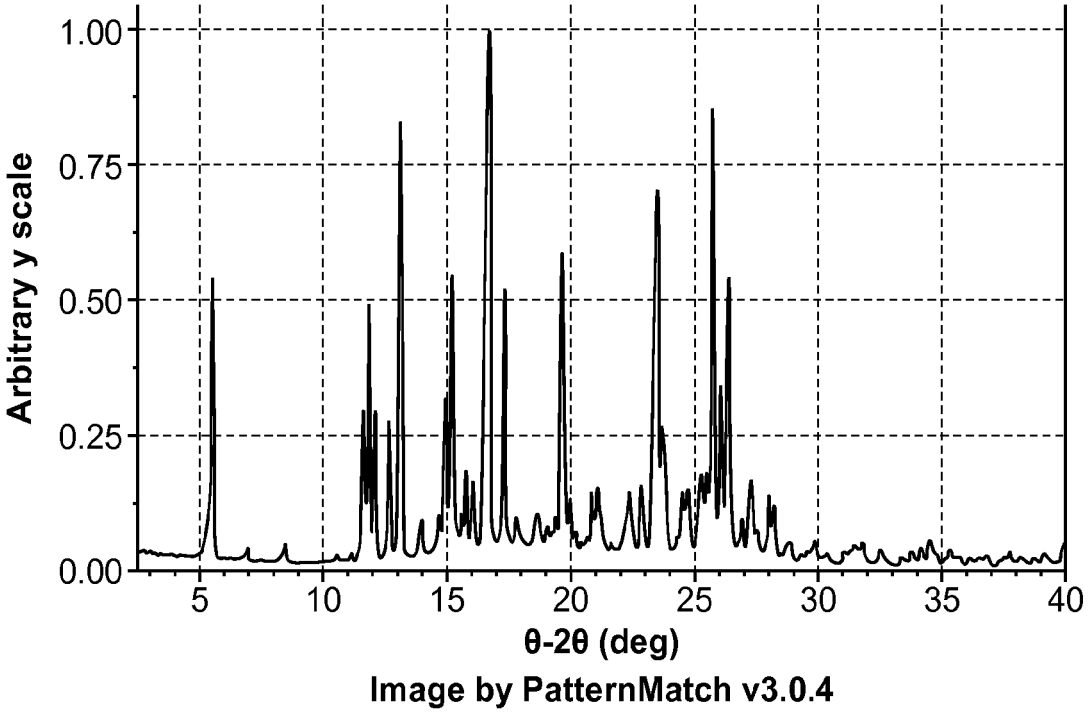
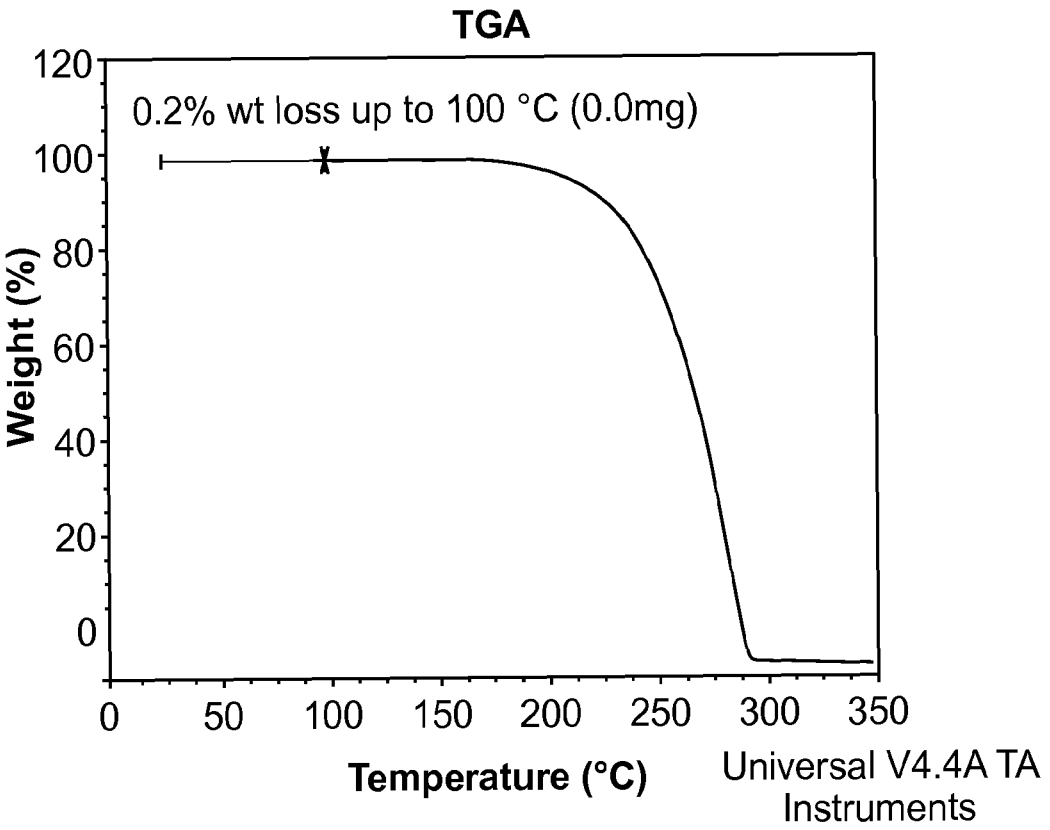

1.00
0.75
0.50
0.25
0.00
Arbitrary y scale
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 7


TGA
0.2% wt loss up to 100 °C (0.0mg)
Weight (%)
120
100
80
60
40
20
0
0
50
100
150
200
250
300
350
Temperature (°C)
Universal V4.4A TA Instruments

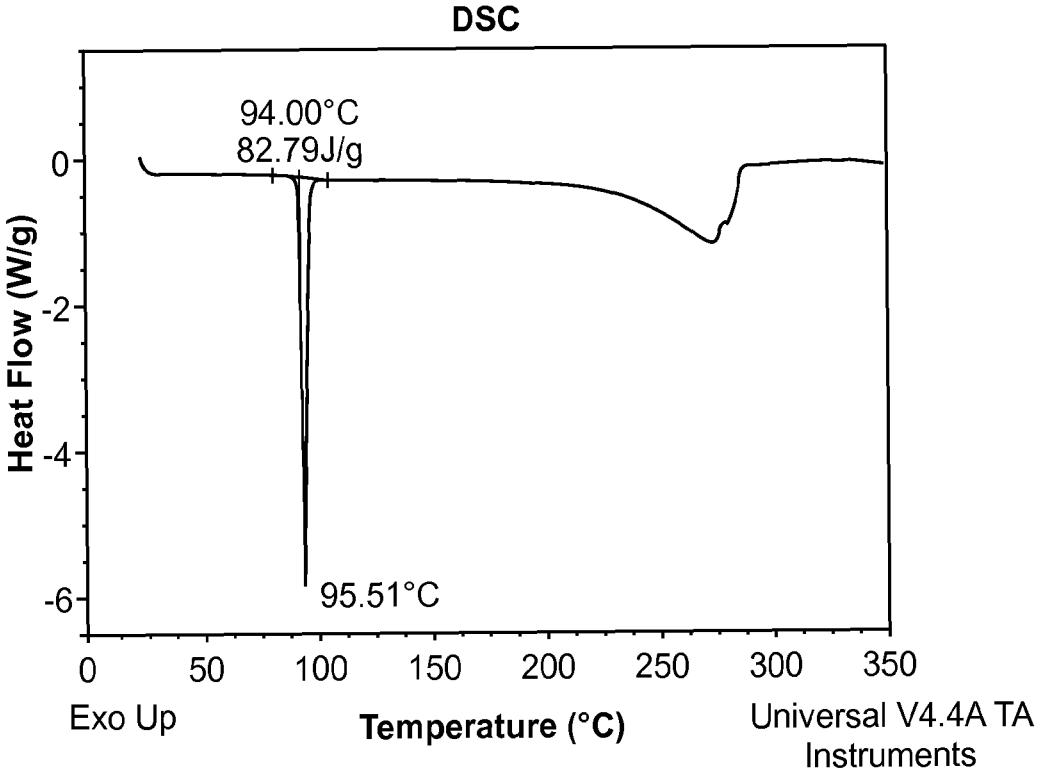

DSC
94.00°C
82.79J/g
95.51°C
Heat Flow (W/g)
0
-2
-4
-6
0
50
100
150
200
250
300
350
Exo Up
Temperature (°C)
Universal V4.4A TA Instruments

FIG. 8

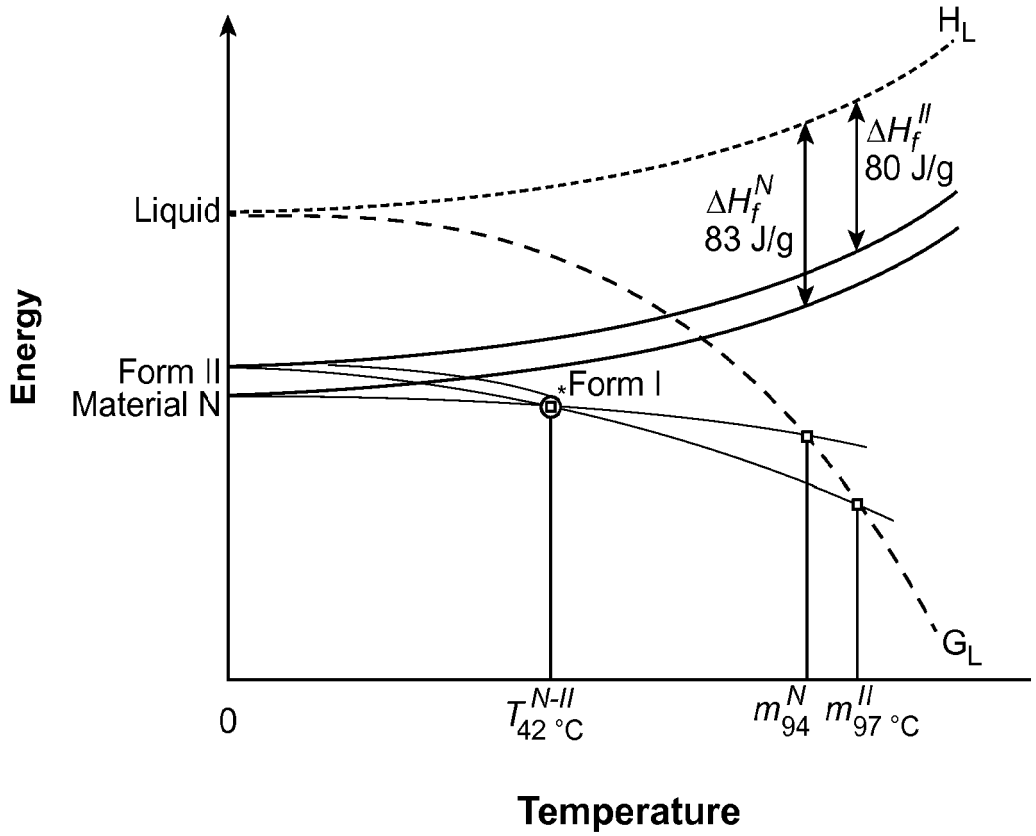

H_L
ΔH_f^II
80 J/g
ΔH_f^N
83 J/g
Liquid
Energy
Form II
Material N
*Form I
G_L
0
T_42 °C^N-II
m_94^N
m_97 °C^II
Temperature

FIG. 9

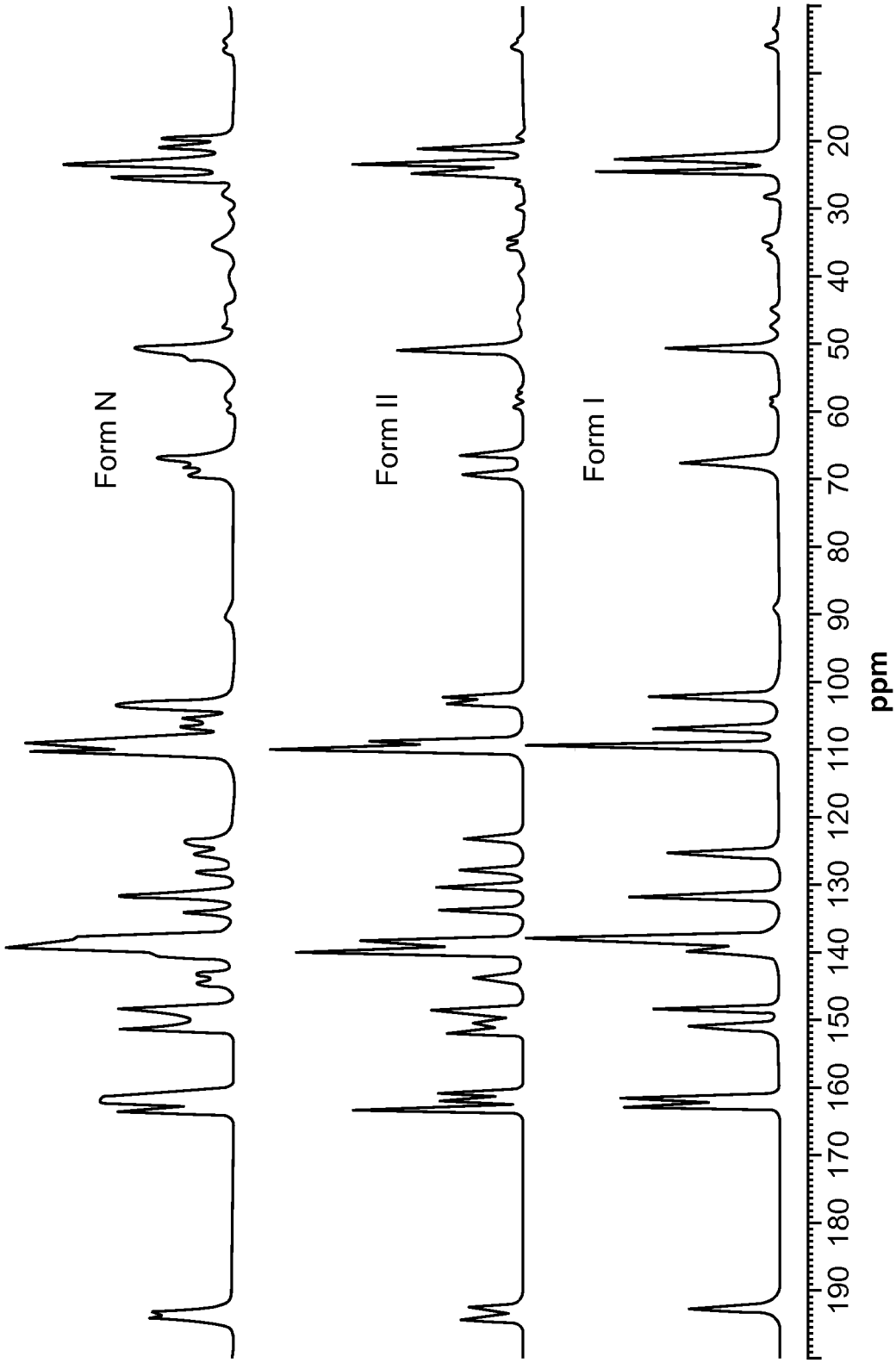

Form N
Form II
Form I
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

FIG. 10

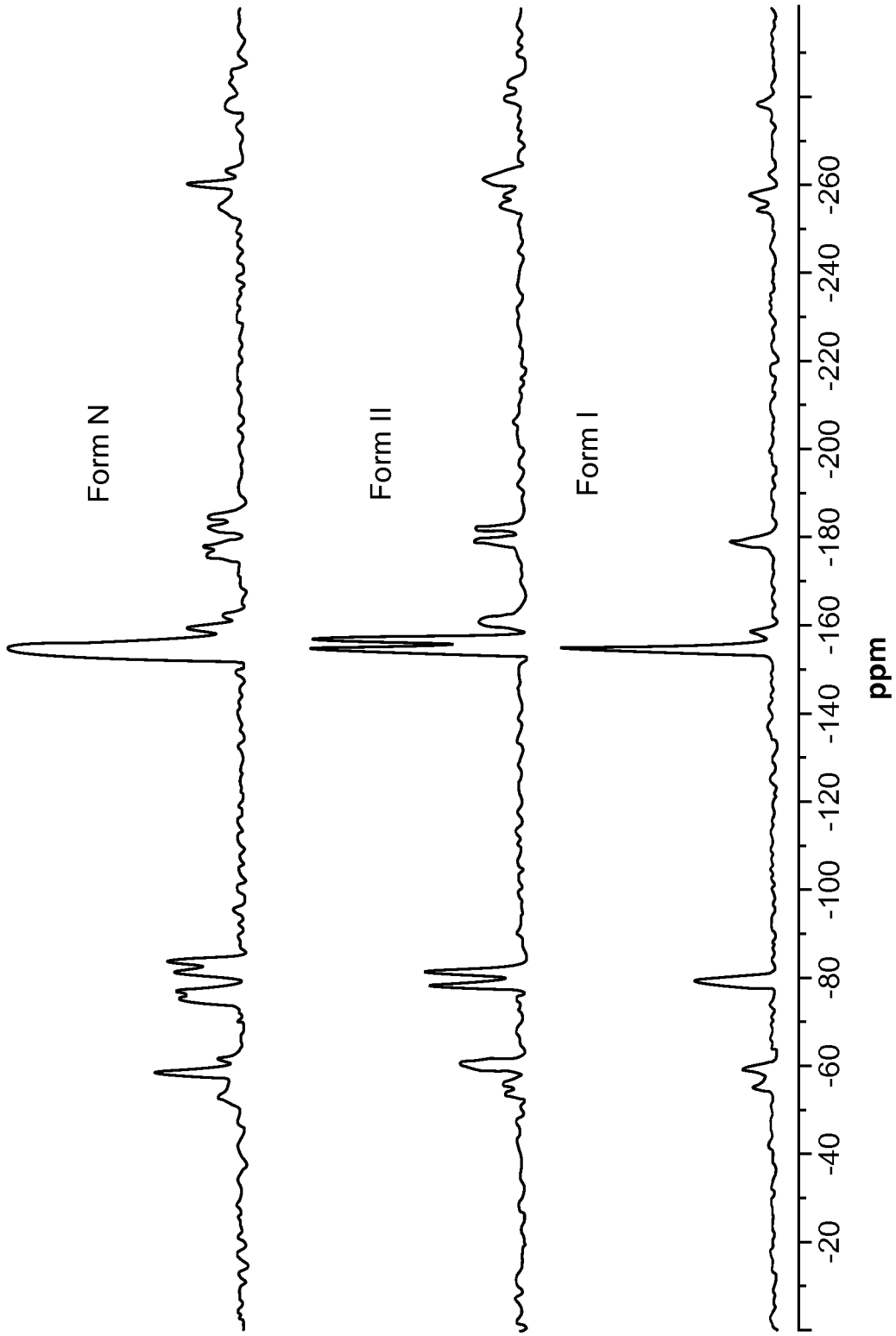

Form N
Form II
Form I
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
ppm

FIG. 11

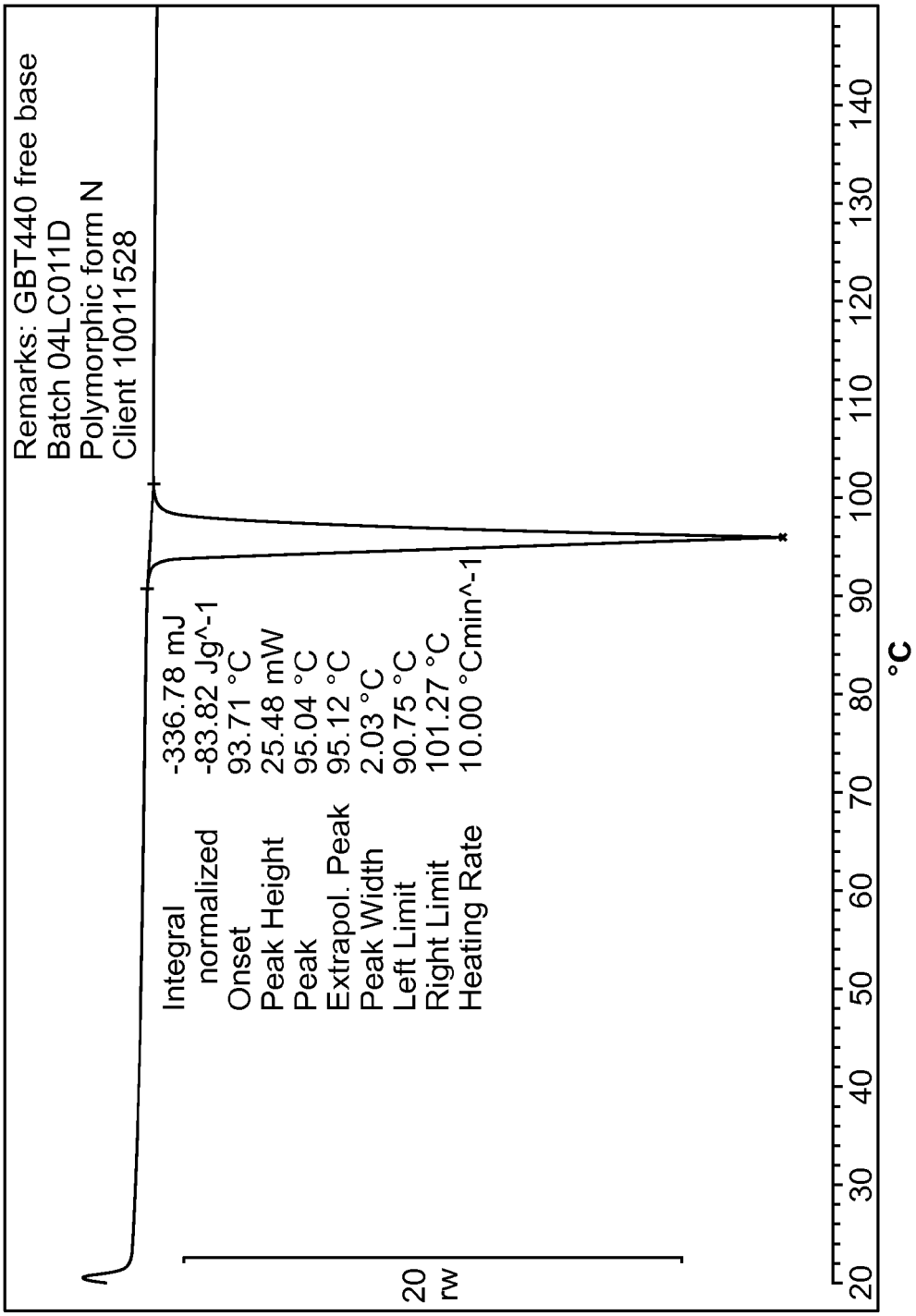

Remarks: GBT440 free base
Batch 04LC011D
Polymorphic form N
Client 10011528
Integral -336.78 mJ
normalized -83.82 Jg^-1
Onset 93.71 °C
Peak Height 25.48 mW
Peak 95.04 °C
Extrapol. Peak 95.12 °C
Peak Width 2.03 °C
Left Limit 90.75 °C
Right Limit 101.27 °C
Heating Rate 10.00 °Cmin^-1
20
rw
20 30 40 50 60 70 80 90 100 110 120 130 140
°C

FIG. 12

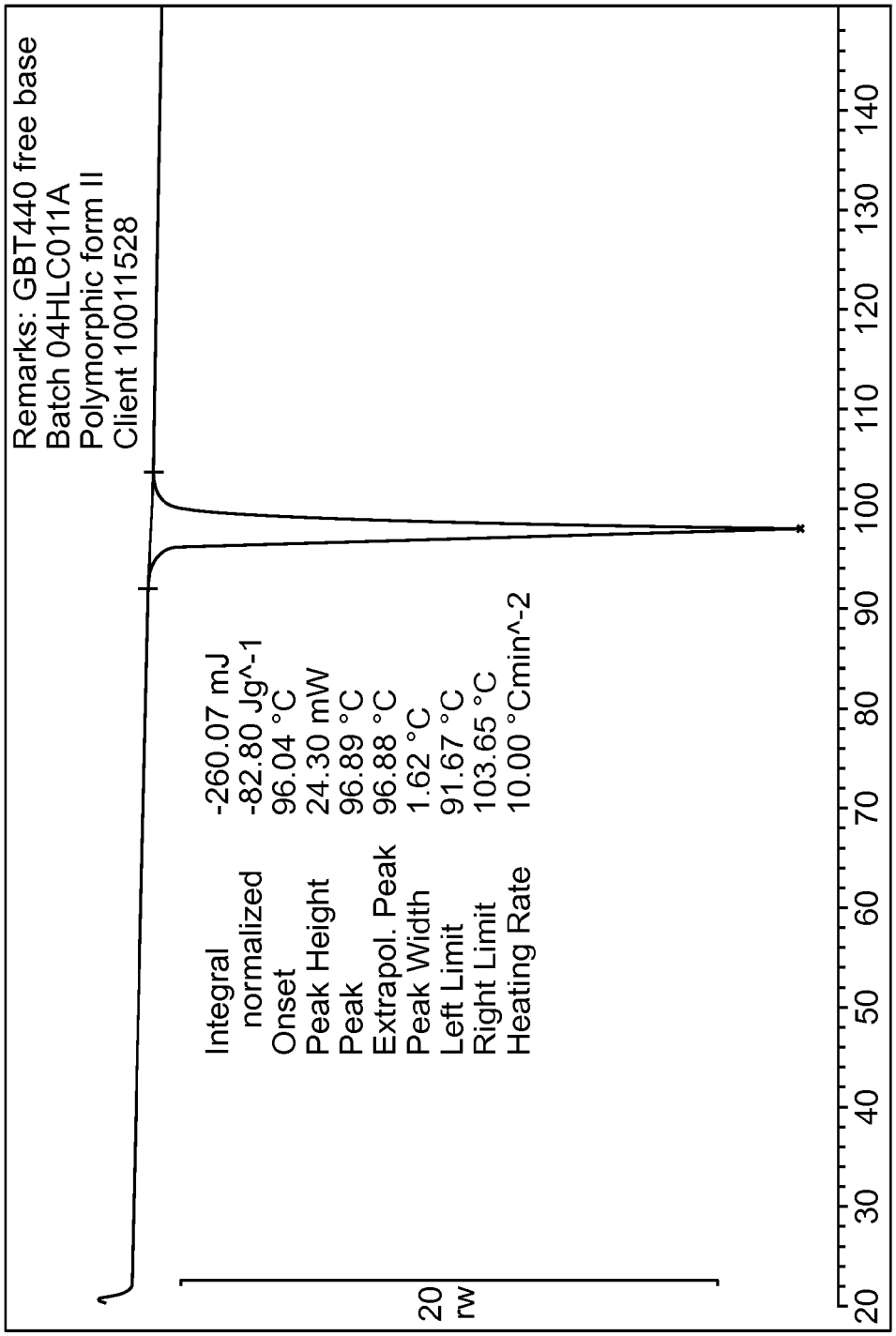

Remarks: GBT440 free base
Batch 04HLC011A
Polymorphic form II
Client 10011528
Integral -260.07 mJ
normalized -82.80 Jg^-1
Onset 96.04 °C
Peak Height 24.30 mW
Peak 96.89 °C
Extrapol. Peak 96.88 °C
Peak Width 1.62 °C
Left Limit 91.67 °C
Right Limit 103.65 °C
Heating Rate 10.00 °Cmin^-2
20
rw
20 30 40 50 60 70 80 90 100 110 120 130 140
°C

FIG. 13

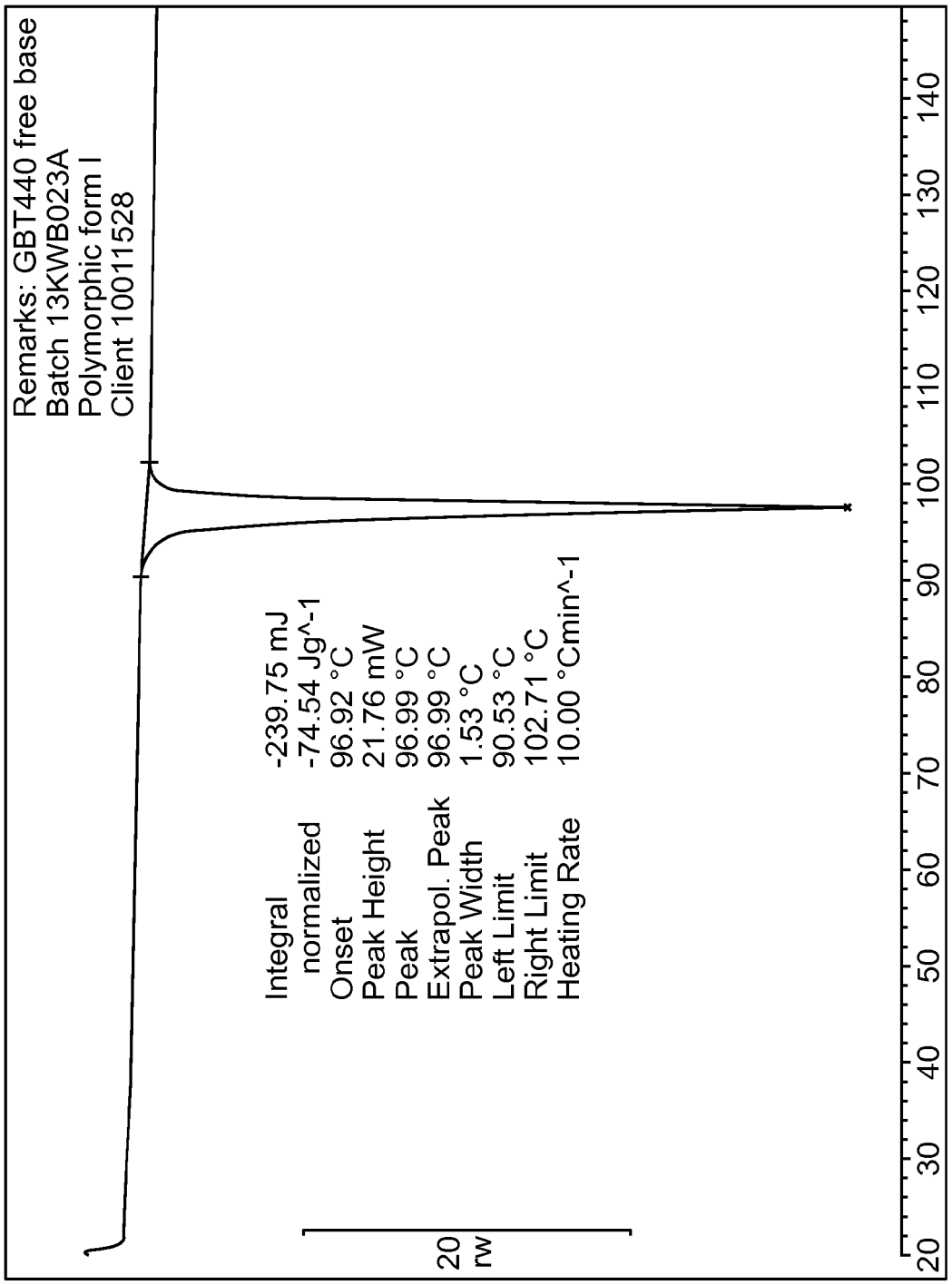

Remarks: GBT440 free base
Batch 13KWB023A
Polymorphic form I
Client 10011528
Integral -239.75 mJ
normalized -74.54 Jg^-1
Onset 96.92 °C
Peak Height 21.76 mW
Peak 96.99 °C
Extrapol. Peak 96.99 °C
Peak Width 1.53 °C
Left Limit 90.53 °C
Right Limit 102.71 °C
Heating Rate 10.00 °Cmin^-1
20
mW
20
30
40
50
60
70
80
90
100
110
120
130
140
°C

FIG. 14

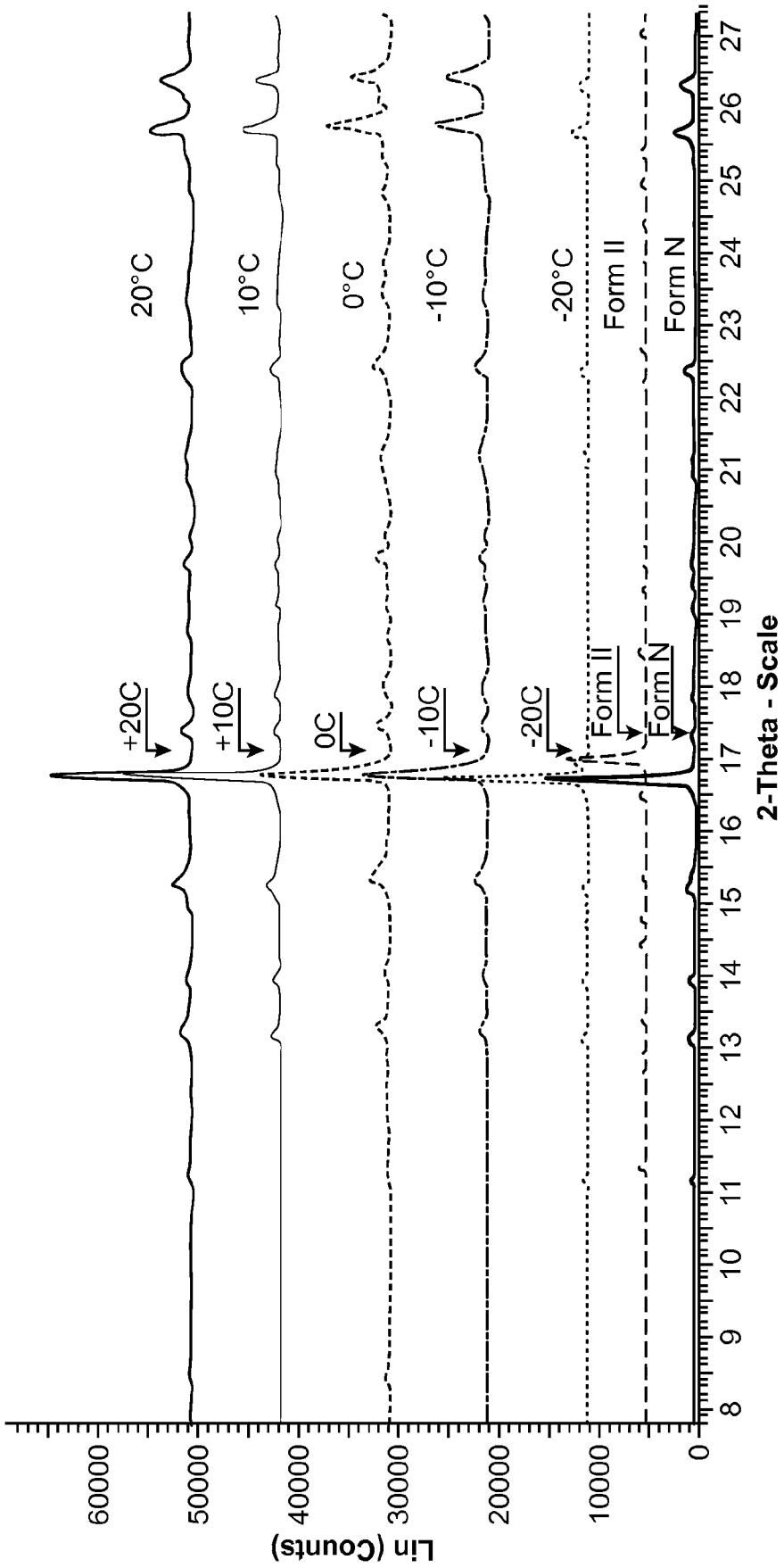
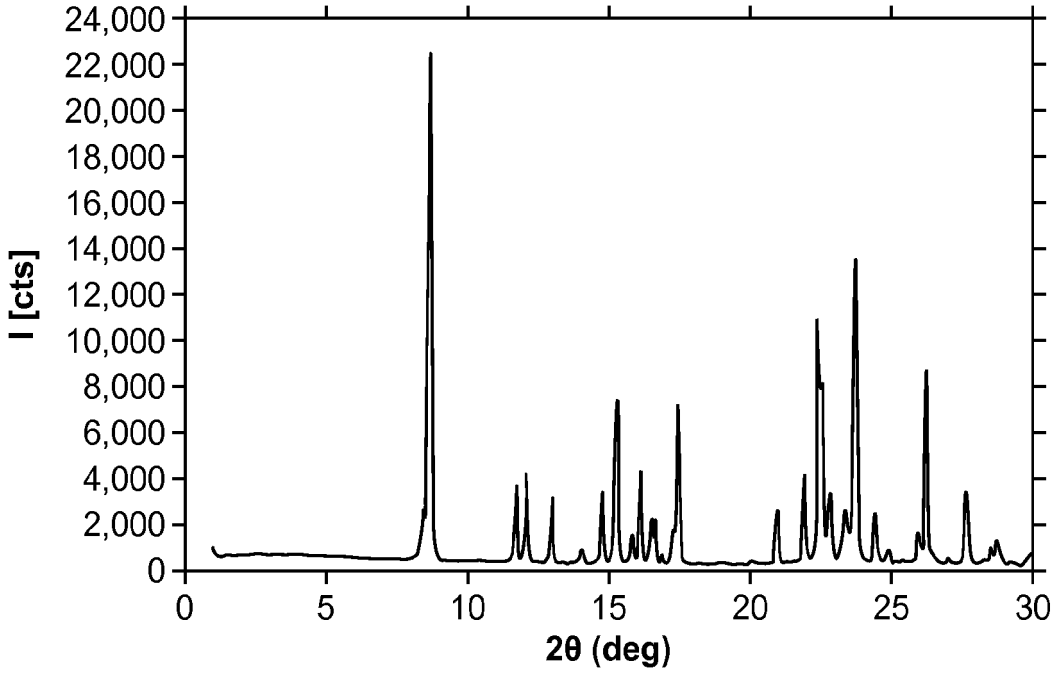
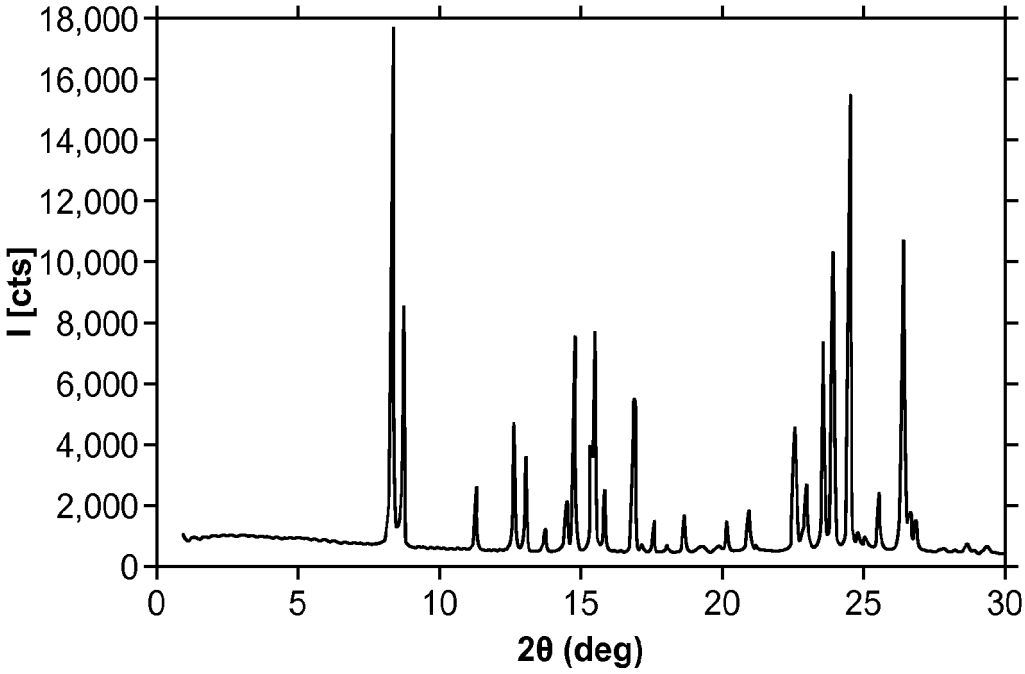

Lin (Counts)
60000
50000
40000
30000
20000
10000
0
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
2-Theta - Scale
+20C
+10C
0C
-10C
-20C
Form II
Form N
20°C
10°C
0°C
-10°C
-20°C
Form II
Form N

FIG. 15



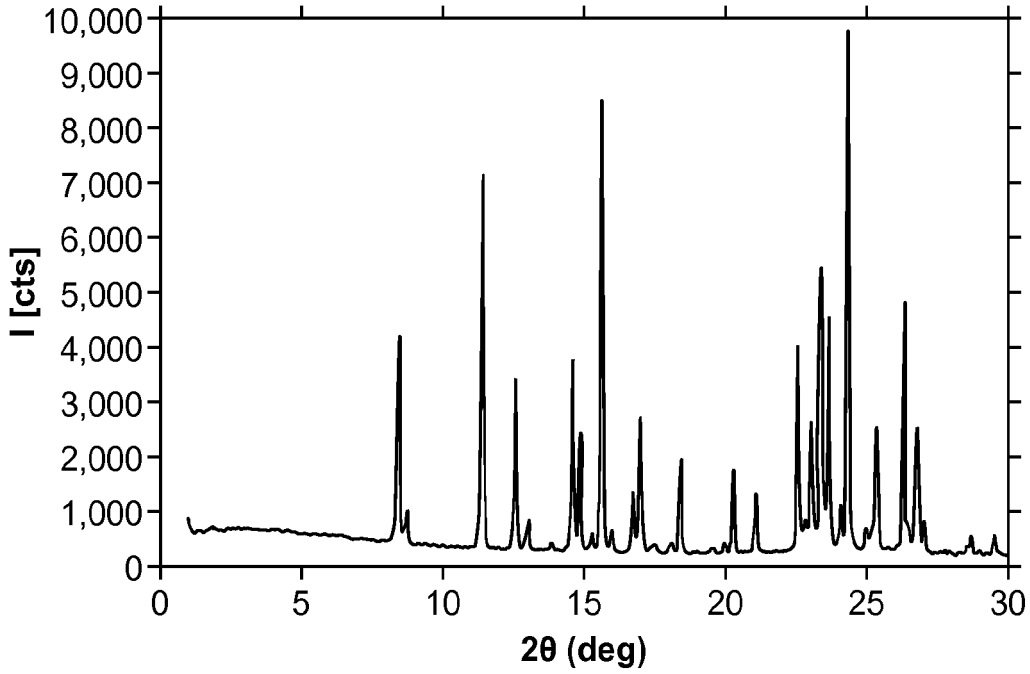
Bravais Type	Triclinic
a [Å]	7.966
b [Å]	11.609
c [Å]	12.382
α [deg]	116.67
β [deg]	104.16
γ [deg]	94.58
Volume [$Å^3$/cell]	968.1
Chiral Contents?	Achiral
Extinction Symbol	P -
Space Group(s)	P1 (1), $P\bar{1}$ (2)
Source	Manual Input

FIG. 16



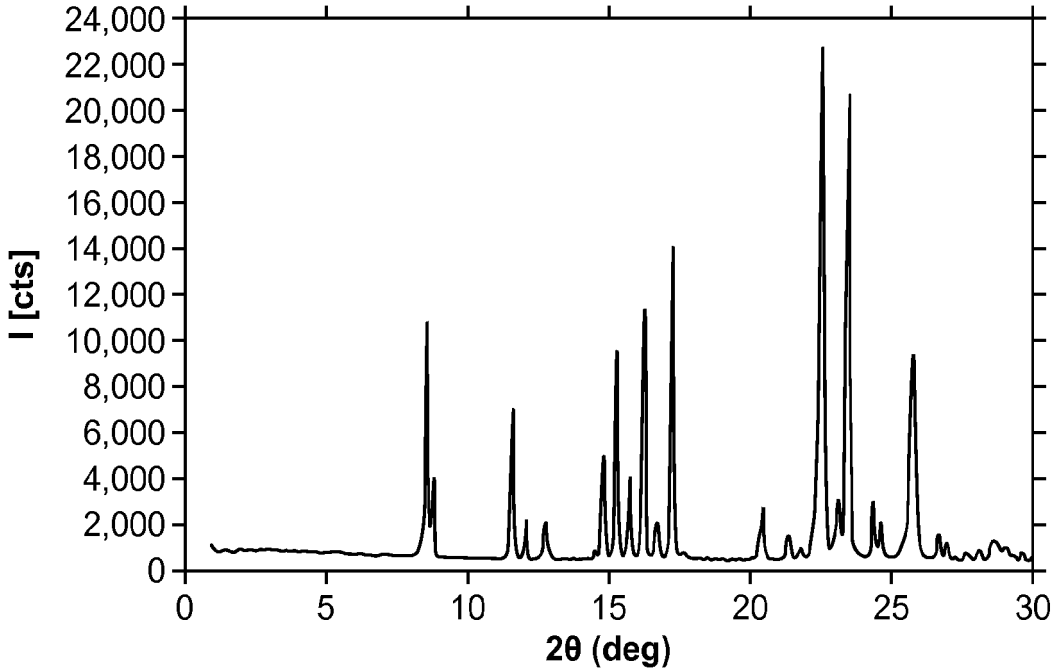
Bravais Type	Triclinic	Triclinic
a [Å]	7.966	7.966
b [Å]	11.726	11.891
c [Å]	11.891	12.031
α [deg]	61.25	121.30
β [deg]	86.34	99.19
γ [deg]	76.79	93.66
Volume [$Å^3$/cell]	946.7	946.6
Chiral Contents?	Achiral	Achiral
Extinction Symbol	P -	P -
Space Group(s)	P1 (1), $P\bar{1}$ (2)	P1 (1), $P\bar{1}$ (2)
Source	Manual Input	Manual Input

FIG. 17



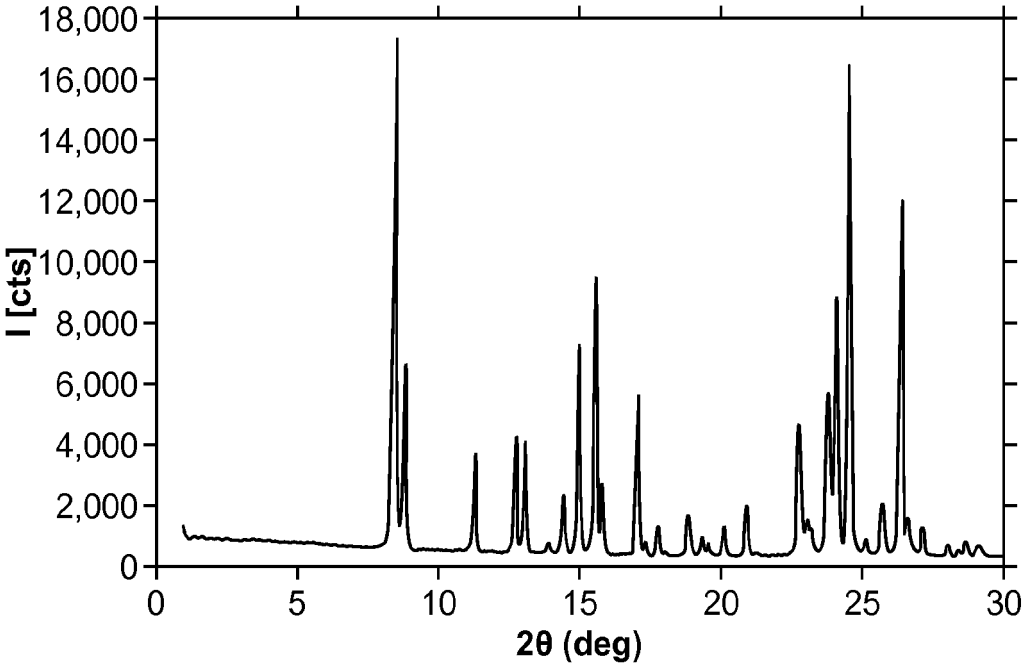
Bravais Type	Triclinic	Triclinic
a [Å]	7.971	7.971
b [Å]	11.901	11.901
c [Å]	11.914	12.131
α [deg]	61.25	120.57
β [deg]	75.84	99.94
γ [deg]	86.05	93.95
Volume [$Å^3$/cell]	959.2	959.2
Chiral Contents?	Achiral	Achiral
Extinction Symbol	P -	P -
Space Group(s)	P1 (1), $P\bar{1}$ (2)	P1 (1), $P\bar{1}$ (2)
Source	Manual Input	Manual Input

FIG. 18



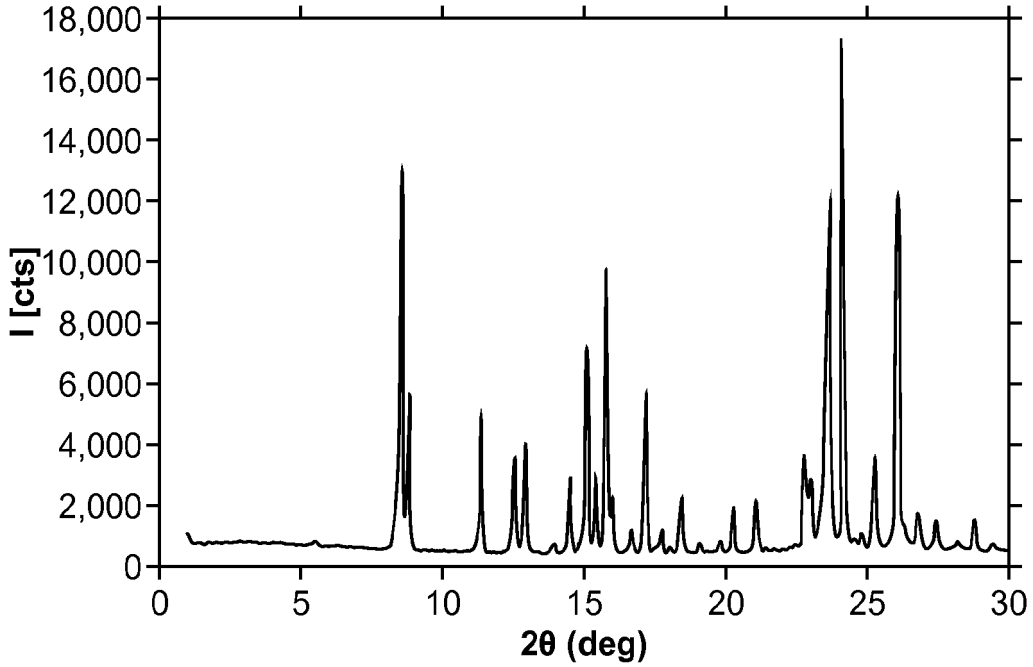
Bravais Type	Triclinic
a [Å]	8.011
b [Å]	11.633
c [Å]	12.471
α [deg]	117.30
β [deg]	102.75
γ [deg]	96.36
Volume [Å^3/cell]	976.7
Chiral Contents?	Not Specified
Extinction Symbol	P -
Space Group(s)	P1 (1), P$\bar{1}$ (2)
Source	Triads Algorithm

FIG. 19



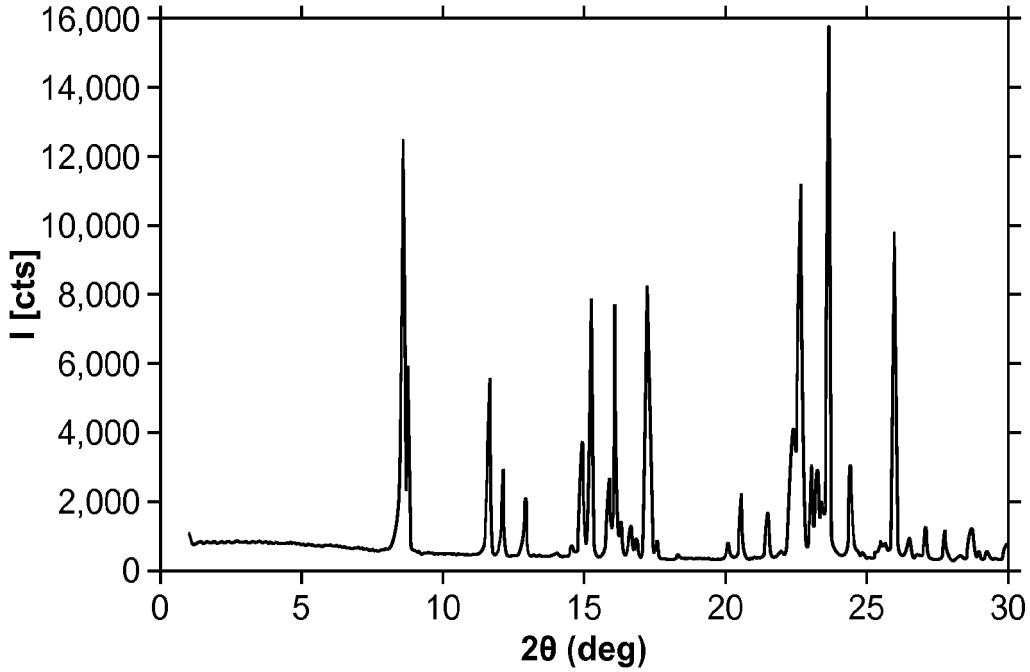
Bravais Type	Triclinic	Triclinic
a [Å]	8.005	8.005
b [Å]	11.676	11.812
c [Å]	11.812	11.974
α [deg]	61.30	121.21
β [deg]	85.79	98.35
γ [deg]	77.10	94.21
Volume [$Å^3$/cell]	943.2	943.2
Chiral Contents?	Achiral	Achiral
Extinction Symbol	P -	P -
Space Group(s)	P1 (1), $P\bar{1}$ (2)	P1 (1), $P\bar{1}$ (2)
Source	Manual Input	Manual Input

FIG. 20



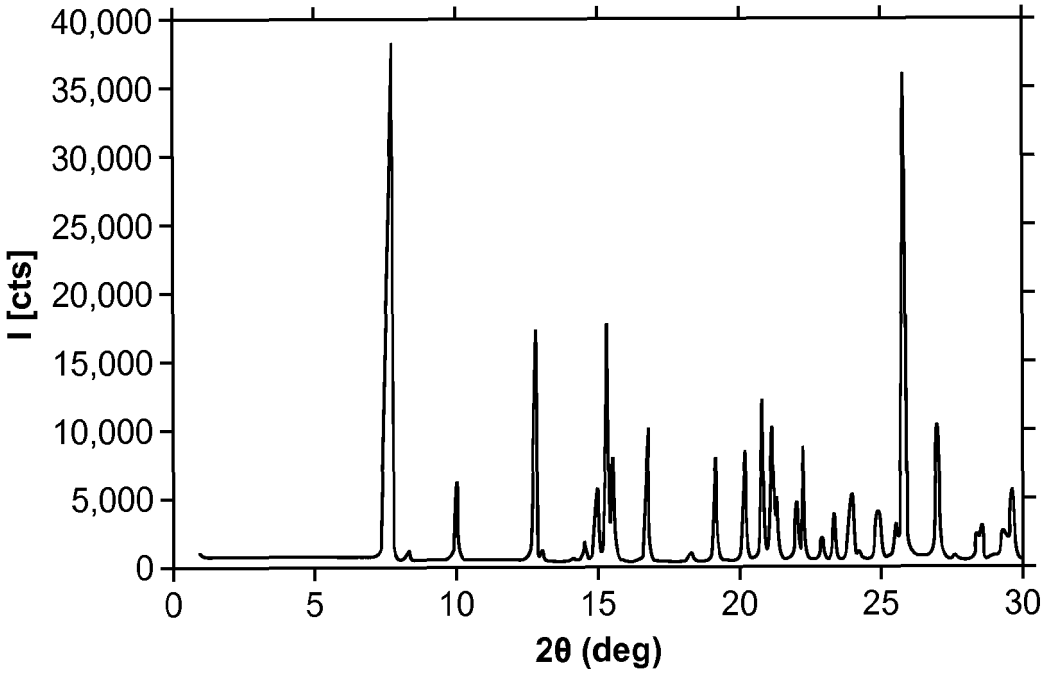
Bravais Type	Triclinic	Triclinic
a [Å]	8.067	8.067
b [Å]	11.820	11.820
c [Å]	11.935	12.096
α [deg]	61.22	120.14
β [deg]	75.17	99.57
γ [deg]	84.93	95.07
Volume [$Å^3$/cell]	963.4	963.4
Chiral Contents?	Achiral	Achiral
Extinction Symbol	P -	P -
Space Group(s)	P1 (1), $P\bar{1}$ (2)	P1 (1), $P\bar{1}$ (2)
Source	Manual Input	Manual Input

FIG. 21



Bravais Type	Triclinic
a [Å]	7.976
b [Å]	11.642
c [Å]	12.429
α [deg]	117.58
β [deg]	102.82
γ [deg]	95.26
Volume [$Å^3$/cell]	971.9
Chiral Contents?	Achiral
Extinction Symbol	P -
Space Group(s)	P1 (1), $P\bar{1}$ (2)
Source	Manual Input

FIG. 22



Bravais Type	C-Centered Orthorhombic	Primitive Monoclinic
a [Å]	13.561	13.801
b [Å]	21.137	13.560
c [Å]	13.790	21.138
α [deg]	90	90
β [deg]	90	90.08
γ [deg]	90	90
Volume [$Å^3$/cell]	3,952.8	3,955.8
Chiral Contents?	Not Specified	Not Specified
Extinction Symbol	C c - -	P 1 2_1/n 1
Space Group(s)	$Ccm2_1$ (36)*, Cc2m (40)*, Ccmm (63)*	$P2_1$/n (14)
Source	Triads Algorithm	Manual Input

* = Unconventional space group setting.

FIG. 23

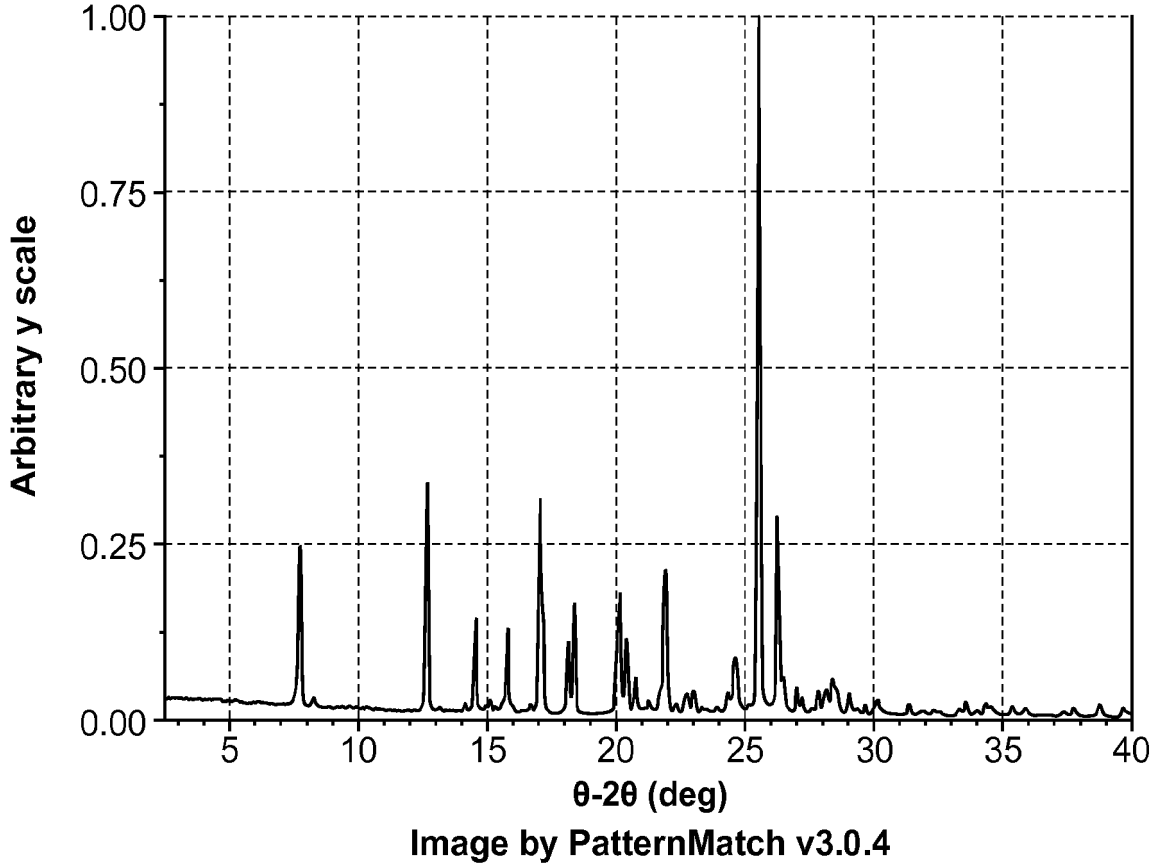

1.00
0.75
0.50
0.25
0.00
Arbitrary y scale
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 24

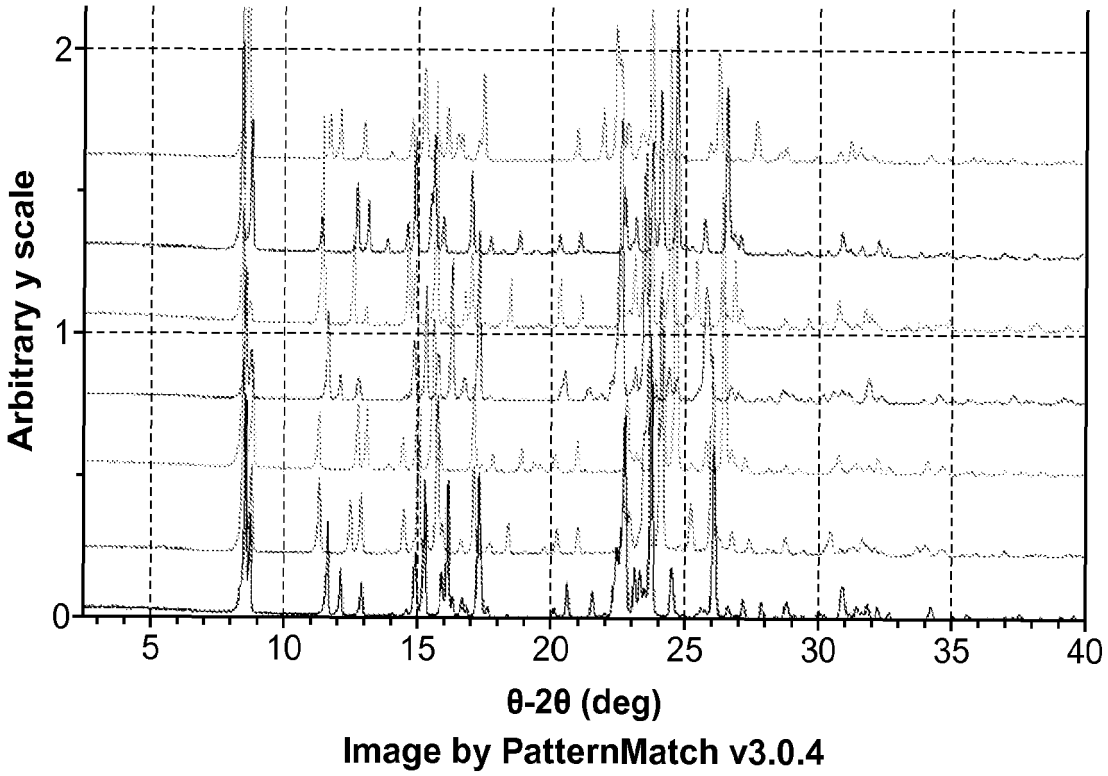

Arbitrary y scale
2
1
0
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 25

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2013102142 A **[0005]**
- US 2013190315 A **[0005]**

Non-patent literature cited in the description

- Remington's Pharmaceutical Sciences. 1980 **[0064]**
- *the Journal of Organic Chemistry,* 2009, vol. 74 (11), 4311-4317 **[0097]**